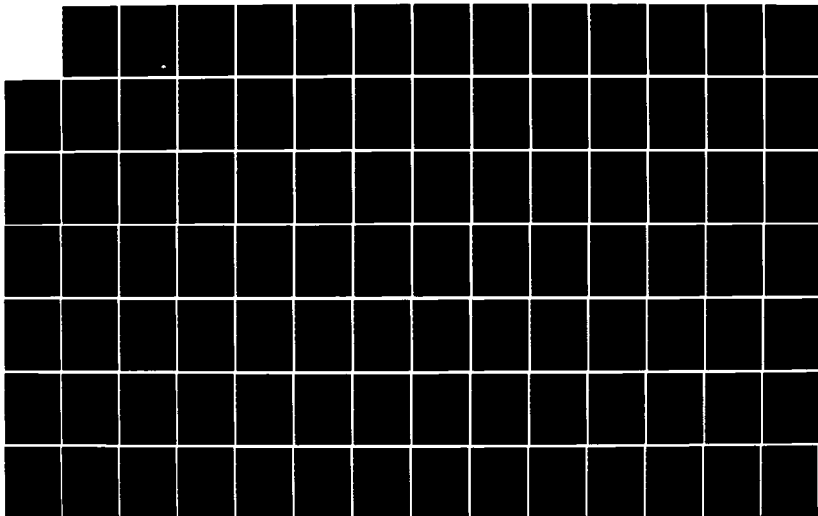AD-A155 113   USAFSAM REVIEW AND ANALYSIS OF RADIOFREQUENCY RADIATION   1/4
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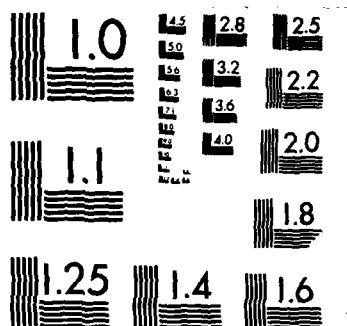   L N HEYNICK ET AL. MAR 85 USAFSAM-TR-85-7
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USAFSAM REVIEW AND ANALYSIS OF RADIOFREQUENCY RADIATION BIOEFFECTS LITERATURE: FIFTH REPORT

Louis N. Heynick, M.S.

Peter Polson, Ph.D.

SRI International
333 Ravenswood Avenue
Menlo Park, California 94025

March 1985

Interim Report for Period 17 March — 31 December 1984

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NOTICES

This interim report was submitted by SRI International, 333 Ravenswood Avenue, Menlo Park, California, under contract F33615-82-C-0610, job order 7757-01-87, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. James H. Merritt (USAFSAM/RZP) was the Laboratory Project Scientist-in-Charge.
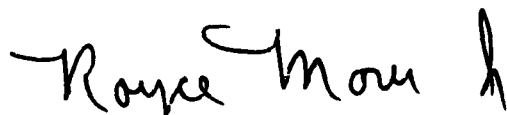
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The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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06	18		

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The objectives of this project are to acquire, review, and analyze on an ongoing basis, information on research pertaining to the biological effects of radiofrequency radiation (RFR) for the preparation of a computer data base of analyses at the USAF School of Aerospace Medicine (USAFSAM). The method in use is to: (1) select documents judged to be representative of prior and current research on various RFR-bioeffects topics, (2) analyze in detail the contents of each such document, and (3) assess the validity and significance of the results presented. In this fifth report, the major RFR-bioeffects topics are listed and the format used for analyzing each selected document is described. During the period covered by this report, 40 additional analyses were completed, for a total of 200 analyses. The texts of the additional analyses are presented in Appendix A. In addition to the text, each analysis includes information for computer retrieval by authors, key words, year of publication, and RFR parameters. Appendixes B and C are two cumulative indexes to reference citations for all of the

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED	
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20. ABSTRACT (concluded)

analyses completed thus far. In Appendix B, each citation is listed under each pertinent
major topic. Appendix C comprises a cumulative list of citations in alphabetical order
by first author and without regard to topic.

CONTENTS

FIGURES

Figure

USAFSAM REVIEW AND ANALYSIS OF RADIOFREQUENCY RADIATION
BIOEFFECTS LITERATURE: FIFTH REPORT

INTRODUCTION

The objectives of this project are to acquire, review, and analyze, on an ongoing basis, information on research pertaining to the biological effects of radiofrequency radiation (RFR), and to provide periodic technical reports of our findings and assessments to the USAF School of Aerospace Medicine (USAFSAM) in specified formats.

The first volume of analyses, for the period from 1 March through 31 August 1980, was issued as Report SAM-TR-81-24 (November 1981). The second volume, for the period from 1 September 1980 through 30 June 1981, was issued as Report SAM-TR-82-16 (May 1982). These two reports were prepared on Contract Number F33615-80-C-0608 (SRI Project 1485). The work is continuing on Contract Number F33615-82-C-0610 (SRI Project 4472). Thus far under the latter contract, the third volume, for the period from 17 May 1982 through 16 June 1983, was issued as Report USAFSAM-TR-84-6 (March 1984); the fourth volume, for the period from 17 June 1983 through 16 March 1984, was issued as Report USAFSAM-TR-84-17 (May 1984). The present (fifth) volume is for the period from 17 March through 31 December 1984.

METHODOLOGY

Thousands of scientific papers, reports, books, summaries, and abstracts (referred to collectively herein as "documents") have been published on the bioeffects of RFR and related fields. Because references to most of these documents are readily available through various abstracting services and data bases, we are endeavoring to avoid needless duplication of such services and information. Instead, we are selecting documents judged to be representative of prior and current research on various RFR-bioeffects topics, analyzing the contents of each such document in detail, and assessing the validity and the significance of the results presented.

The primary task of the project is to prepare an analysis of each selected document in a specified format for computer storage and retrieval by any of a variety of designators: analysis number, major bioeffects topic, author(s), year of publication, frequency, power density, modulation, duty cycle, specific absorption rate (SAR), species, and special key words. The software for retrieval is being developed by USAFSAM.

The analyses in the first two volumes were printed with an optical-character-recognition (OCR-B) font, to permit direct computer input of the information by any recipient of the volumes without retyping. This practice was found to be technically deficient, so it was discontinued for subsequent volumes. Inclusion of International

Standard Serial Numbers (ISSNs) in the citations was also discontinued. In addition, the initial analysis format used was modified to conform with USAFSAM's retrieval software. The outline form now in use for analyses is displayed in Figure 1.

To conform with the modified format, numbers 1 through 80 were assigned serially to the analyses in the first two volumes, and the sequence was continued in the subsequent volumes. The authors, title (in upper case), and reference are given immediately after the analysis number. The single asterisk after the citation is a flag to permit retrieval of only the citation part of the analysis, if desired.

As part of each analysis, the abstract or summary provided by the authors is reproduced directly after the citation and the heading "AUTHOR ABSTRACT" or "AUTHOR SUMMARY" is used. If the document does not contain an abstract or summary, its important contents are summarized as given, i.e., without comment, and the heading "REVIEWER SUMMARY" is used to indicate this fact. The two asterisks following the abstract or summary comprise a flag to permit retrieval of only the citation and abstract or summary, if desired.

Next, for each document reviewed, one or more pertinent major topics are listed under "Study type." To conform better with current usage, the list of topics was modified as shown in Figure 2, beginning with the third volume. Also indicated under this heading are whether the study was done in vivo or in vitro and the species involved.

Under the heading "Effect type," the specific effects, phenomena, biological endpoints, or other characteristics studied or sought (but not necessarily found) are listed briefly. The frequencies, modulation characteristics (CW, amplitude-modulation, or pulse parameters), power densities, and SARs are given under their respective headings.

In the next section, "EXPOSURE CONDITIONS," the salient features of the exposure arrangements and parameters are briefly summarized.

Under "OTHER INFORMATION," important information in the text of the document is summarized, again without comment.

Our analysis of the document is given under "CRITIQUE." To the extent possible or appropriate, each critique includes evaluation of the data presented (including the statistical aspects if the data presented are adequate), the biological and engineering methodology used, the validity of the results, how the findings compare with those of other studies, and the significance of the findings with respect to the health of humans (and/or other species) exposed to RFR.

Analysis number
Authors
Title
Citation

*

Author abstract (or reviewer summary)

**

Study type (bioeffects topic; in vivo/in vitro; species)
Effect type
Frequency
Modulation
Power density
SAR

Exposure conditions

Other information

Critique

References

***

[Retrieval information (one entry per line):]
Authors (last names only)

/

Key words

//

Year of publication
Frequency--value or range in MHz (0=unknown)
Duty cycle--value or range (CW=1; 0=unknown)
Power density--average value or range in mW/sq cm (0=unknown)
SAR--average value or range in W/kg (0=unknown)

///

Figure 1. Outline form for analyses.

Auditory Effects
Behavior
Biorhythms
Cardiovascular Effects
Cellular and Subcellular Effects
Endocrinology
Environmental Factors
Exposure Methods, Dosimetry, and Modeling
Human Studies
Immunology and Hematology
Mechanisms of Interaction
Medical Applications
Metabolism and Thermoregulation
Multiagent Interactions
Mutagenesis, Carcinogenesis, and Cytogenetic Effects
Nervous System
Ocular Effects
Physiology and Biochemistry
Teratology and Developmental Abnormalities

Figure 2.   Type of study.

It should be noted that critiques in the first two volumes were labeled "INITIAL" or "FINAL," a practice that was discontinued with the third volume in consonance with the view that any critique should be subject to possible revision, e.g., updates based on subsequent information or comments from the authors of the document. Concerning the latter point, written comments from authors or others regarding any analysis are welcome and will be treated as addenda to the critique thereof.

Any literature citations mentioned in the analysis are shown under "REFERENCES." The three asterisks after the references section mark the end of the analysis proper and comprise a flag to permit retrieval of the full text of the analysis proper.

The following items are for retrieval of the analysis by any of various designators. Listed first are the last names individually of all the authors of the document, followed by a single slant sign (/) to indicate the end of this form of designator. Key words derived from the analysis of the document comprise the next set of designators. Such key words are not necessarily those provided by the authors, but are from a list designed expressly for USAFSAM retrieval use. The current list is displayed in Figure 3. It includes one addition, "APLYSIA," to the list in the previous volume. Other additions to the list may be made as appropriate. This designator section is terminated with two slant lines (//).

6

ANTIGEN
ANTIBODY
APLYSIA
AUDITORY
BACTERIA
BEHAVIOR
BIOCHEMISTRY
BIORHYTHM
BBB
BRAIN-UPTAKE-INDEX
CALCIUM
CARCINOGENIC
CARDIOVASCULAR
CAT
CELLULAR
CHICKEN
CHINCHILLA
CHRONIC
CIRCADIAN
COMPLEMENT
CORTICOSTEROID
CW
CYTOGENETIC
DEVELOPMENT
DIELECTRIC
DOG
DOSIMETRY
DROSOPHILA
DRUG-RFR
E-COLI
ECOLOGICAL
EEG
EFFLUX
EKG
EMBRYO
ENDOCRINOLOGIC
ENVIRONMENTAL
EPIDEMIOLOGIC
ESTRUS
EVOKED-POTENTIAL
EXPOSURE-SYSTEM
FROG
GUINEA-PIG
HAMSTER
HAPLOTYPE
HEMATOLOGY
HISTOLOGY

HUMAN
HYPERTHERMIA
HYPOTHERMIA
IMMUNOLOGY
INFLAMMATION
INSTRUMENTATION
IN-VITRO
IN-VIVO
LETHALITY
LEUKOCYTE
LYMPHOCYTE
MECHANISMS
MEDICAL
METABOLISM
MICROSCOPY
MITOGEN
MODEL
MODULATED
MONKEY
MORBIDITY
MORTALITY
MOUSE
MULTIAGENT
MUTAGENIC
NERVOUS-SYSTEM
OCCUPATIONAL
OCULAR
PHYSIOLOGY
POSITIVE-CONTROL
PRIMATE
PULSED
QUAIL
RABBIT
RAT
RECTAL
REPEATED-ACQUISITION
REVIEW
RFR
STRESS
TENEBRIO
TERATOGENIC
THERMOREGULATION
THRESHOLD
TRACER
TURTLE
WEIGHT
YEAST

Figure 3. List of key words.

7

In the final section of designators, the following information is presented in sequence: the year of publication of the document; the frequency or frequency range of the RFR in MHz; the duty cycle or range thereof, with "1" representing continuous-wave (CW) RFR or amplitude-modulated RFR when appropriate; the average power density or its range in mW/sq cm; and the average SAR or its range in W/kg. (Peak power density is not included as a designator because values thereof can be calculated from duty cycles and average power densities.) The symbol "0" is used to signify "unknown" or "not specified". This designator section is terminated with three slant lines (///), which also indicate the end of the entire analysis, including the retrieval information.

The analyses in Appendix A to this volume illustrate this methodology.

PROGRESS DURING THIS PERIOD

By the end of this period, 40 additional analyses were completed, for a total of 200 in the five reports. The texts of these 40 analyses (including the retrieval data) are presented in sequence by analysis number in Appendix A.

As in the previous volume, two cumulative indexes to reference citations for all of the analyses completed thus far are included in this volume. In Appendix B, each citation is listed under each of the pertinent major topics (selected from Figure 2) shown under "Study Type" in the analysis. Appendix C comprises a cumulative list of citations, in alphabetical order by first author and without regard to topic, for all analyses completed. For ease in finding the text of any analysis from either list, the five volumes are referred to by Roman numerals in chronological succession, and the end of each reference citation in each cumulative list is annotated with the Roman numeral of the volume containing the text of the analysis, followed by the first page number of the text. This indexing method is illustrated below:

87
Galvin, M.J., D.I. McRee, and M. Lieberman
EFFECTS OF 2.45-GHZ MICROWAVE RADIATION ON EMBRYONIC QUAIL HEARTS
Bioelectromagnetics, Vol. 1, No. 4, pp. 389-396 (1980) (III-35)

This citation is listed in Appendix B under the topic headings Cardiovascular Effects, Physiology and Biochemistry, and Teratology and Developmental Abnormalities, and is shown under "Galvin..." in Appendix C. The annotation "III-35" indicates that the analysis of this document can be found on page 35 of the third volume.

PROPOSED PLANS FOR THE FUTURE

The data base produced thus far under this project will be augmented by the preparation of detailed analyses of other important documents on biological effects of RFR.

A revision is under way of "Bioeffects of Radiofrequency Radiation: A Review Pertinent to Air Force Operations," by L.N. Heynick and P. Polson, which was issued as USAFSAM Report SAM-TR-83-1 (March 1983). The revised document will include analyses of publications and other pertinent information that postdate the issuance of the review.

ACKNOWLEDGMENTS

Again, we are grateful for the contributions to this project of Barrett P. Eynon, Statistician, Data Design and Analysis Department of SRI's Health and Social Systems Division, and we appreciate the efforts of Judith Bull, Senior Library Assistant, in obtaining copies of not readily available documents.

FREY
SEIFERT

/

BIORHYTHM
CARDIOVASCULAR
EKG
FROG
IN-VITRO
PULSED
RFR

//

1968
1425
0.00001
0.0006
0

///

beat rates of isolated frog hearts. In addition, Liu et al. (1976) obtained negative results from similar exposures in-vivo of frog hearts in-situ. More recently, Chou et al. (1980b) obtained no effects on the heart rates of intact rabbits exposed to 10-microsecond pulses of 2.45-GHz RFR at a pulse power density of 13.7 W/sq cm. Thus, little credence can be given to the findings of Frey and Seifert (1968).

REFERENCES:
Chou, C.-K., L.F. Han, and A.W. Guy
MICROWAVE RADIATION AND HEART-BEAT RATE OF RABBITS
J. Microwave Power, Vol. 15, No. 2, pp. 87-93 (1980b)

Clapman, R.M. and C.A. Cain
ABSENCE OF HEART-RATE EFFECTS IN ISOLATED FROG HEART IRRADIATED WITH
PULSE MODULATED MICROWAVE ENERGY
J. Microwave Power, Vol. 10, No. 4, pp. 411-419 (1975)

Levitina, N.A.
NONTHERMAL ACTION OF MICROWAVES ON THE CARDIAC RHYTHM OF THE FROG
Bull. Exp. Biol. Med., Vol. 62, No. 12, pp. 1386-1387 (1966)
(Engl. Transl. of pp. 64-66 of 1966 Russ. publ.)

Liu, L.M., F.J. Rosenbaum, and W.F. Pickard
THE INSENSITIVITY OF FROG HEART RATE TO PULSE MODULATED MICROWAVE ENERGY
J. Microwave Power, Vol. 11, No. 3, pp. 225-232 (1976)

Presman, A.S. and N.A. Levitina
NONTHERMAL ACTION OF MICROWAVES ON CARDIAC RHYTHM--COMM. I: A STUDY OF
THE ACTION OF CONTINUOUS MICROWAVES
Bull. Exp. Biol. Med., Vol. 53, No. 1, pp. 36-39, (1963a)
(Engl. Transl. of pp. 41-44 of 1962a Russ. publ.)

Presman, A.S. and N.A. Levitina
NONTHERMAL ACTION OF MICROWAVES ON THE RHYTHM OF CARDIAC CONTRACTIONS IN
ANIMALS--REP. II: INVESTIGATION OF THE ACTION OF IMPULSE MICROWAVES
Bull. Exp. Biol. Med., Vol. 53, No. 2, pp. 154-157 (1963b)
(Engl. Transl. of pp. 39-43 of 1962b Russ. publ.)

***

reported observing bradycardia in intact frogs exposed to 12.5-cm RFR pulses. Frey and Seifert reasoned that the effects of RFR might be more clearly delineated by exposing isolated hearts to RFR pulses at a lower frequency, the latter because of the greater penetration depth.

Between experimental sessions, Frey and Seifert measured the power density with a quarter-wave dipole connected to a commercial thermistor and power meter.

The results for the sessions involving the 200-millisecond delay after the peak of the P wave (i.e. roughly coincident with the occurrence of the QRS complex) were presented in Table 1 of the paper in terms of relative change of beat rate (in arbitrary units) for each period of 5 hearts subjected to the first protocol (exposure during period II only) and 3 hearts given the second protocol.

Of the 5 hearts exposed during period II, 2 exhibited arrythmia for period II and cessation of beating for period III, 1 heart was arrythmic for periods II and III, and the remaining 2 exhibited tachycardia for period II. Of the 3 hearts exposed to RFR during periods I and III, 2 exhibited tachycardia and the third arrythmia for periods I and III. The authors characterized arrythmia and cessation of beating as extreme forms of tachycardia. They stated that use of the two-tailed Wilcoxon matched-pairs, signed-rank test showed the results to be significant at the 1% level but presented no statistical data.

The authors also stated: "It could be argued from the remaining data that illumination at the occurrence of the P wave or 100 msec after it also effected heart rate. The investigators, though, consider the data on the 0 delay and 100 ms delay to be inconclusive. If an effect exists, it requires more than a small number of preparations to tease it out and to reach statistical significance." (No data were presented.)

Also reported by the authors (without data) was the absence of the effect in the first control group (for which RFR-absorbent material was interposed between the heart and the horn), and that the results for the second control group (for which voltage pulses up to 100 times higher and 1000 times longer than those induced by the RFR pulses were applied to the electrodes) indicated that the effect could not be attributed to such induction.

CRITIQUE: The paucity of subjects, the absence of data for the control groups, the obscurity of those data presented (numerical values given in arbitrary, undefined units unaccompanied by uncertainty values), and the absence of any statistical treatment of the results (other than statements regarding such treatment) render it difficult to assess the validity of the findings of this investigation or to compare them with those of other investigators.

Clapman and Cain (1975) and Liu et al. (1976) endeavored to repeat the experiments of Frey and Seifert and were not able to detect any effects of synchronized pulses of 1.42-GHz RFR (without and with delays) on the

163
Frey, A.H. and E. Seifert
PULSE MODULATED UHF ENERGY ILLUMINATION OF THE HEART ASSOCIATED WITH
CHANGE IN HEART RATE
Life Sci., Vol. 7, No. 10, Part II, pp. 505-512 (1968)

*

AUTHOR SUMMARY: Recent reports indicate that illumination with UHF
energy affects the heart and CNS. Isolated frog hearts were illuminated
with pulse modulated UHF energy in this investigation. The pulses were
synchronized with the ECG in an attempt to induce a positive feedback
condition. Statistically significant changes in heart rhythm were
associated with the UHF illumination. It was concluded that more
extensive investigations were warranted.

**

Study Type: Cardiovascular Effects, Biorhythms; IN VITRO; FROG
Effect Type: Effects of synchronized RFR pulses on heart rate
Frequency: 1.425 GHz
Modulation: 10-microsecond pulses at about 1 pps (0.00001 duty cycle)
Power Density: 60 mW/sq cm Pk, 0.6 microwatts/sq cm Av
SAR: Not determined

EXPOSURE CONDITIONS: Platinum electrodes on a Lucite mount within a
chamber of RFR absorbent material were used to support the isolated
heart dorsal side up and to record the EKG. A subminiature coaxial
cable connected the electrodes to the instrumentation. The section of
cable within the chamber was perpendicular to the E vector. After
decapitating the frog, the heart was removed, mounted with its long axis
parallel to the E vector, moistened with frog Ringer's solution, and
checked for stable beat rate.

Each EKG recording session consisted of three periods (I, II, and III)
of 250 beats each. The two protocols were to expose the heart to RFR:
1) only during period II, and 2) during periods I and III but not II.
During the exposure periods, each P wave of the EKG was used to trigger
a 10-microsecond pulse of 1.42-GHz RFR, which was delivered by a horn
within the chamber at the peak of the P wave (without delay) or with a
delay of 100 or 200 milliseconds.

Two control groups were included. In one, sessions were conducted with
RFR-absorbent material interposed between the heart and the RFR horn.
In the other, electric pulses were fed to the electrodes to simulate
and ascertain the effects of currents induced on the electrodes by the
RFR pulses.

OTHER INFORMATION: The authors noted that Presman and Levitina (1962a,
1962b) had found that with rabbits, in-vivo exposure of the head to
10-cm or 12.5-cm RFR pulses produced tachycardia and exposure of the
body resulted in bradycardia. Also noted was that Levitina (1966) had

Kaplan, I.T., W. Metlay, M.M. Zaret, L. Birenbaum, and S.W. Rosenthal
ABSENCE OF HEART-RATE EFFECTS IN RABBITS DURING LOW-LEVEL MICROWAVE
IRRADIATION
IEEE Trans. Microwave Theory and Tech., Vol. 19, No. 2, pp. 168-173
(1971)

***

LIU
ROSENBAUM
PICKARD

/

BIORHYTHM
CARDIOVASCULAR
EKG
FROG
IN-VITRO
IN-VIVO
MULTIAGENT
PULSED
RFR

//

1976
1400-10000
0.0001
0
0

///

Among the interesting points made was their use of curarization prior to heart removal instead of decapitation (used by Frey and Seifert). They noted that d-tubocurarine is known to: affect classical heart rate conditioning in the rat; prevent certain bradyarrhythmias, exert stabilizing actions, or increase the heart rate in humans under various circumstances; or produce a variety of mild effects in sympathetic ganglion cells of the frog (citing various references for these effects). They suggested the possibility "that d-tubocurarine suppressed what otherwise might have been an unmistakable sensitivity to microwaves".

CRITIQUE: The negative results for the in-situ exposures appear to be unequivocal, in view of the negligibly small and nonconsistent period-to-period differences shown for each heart in Tables 2 and 3. With regard to the isolated hearts, however, for which apparently consistent period-to-period bradycardia was evident in Tables 4 and 5, it is not clear whether for comparisons, data were also taken on hearts that were sham-exposed during all three periods. That such was the case was implied in the quote above in connection with Tables 4 and 5, but the absence of such data in the paper renders it difficult to assess the validity of these results. Specifically, if monotonic bradycardia for periods I, II, and III was observed for sham-exposed isolated hearts as well as for the 16 hearts shown in those tables, then the conclusion that the RFR had no significant effect could be sustained. If not, then averaging the values for periods I and III was not justified.

Another uncertainty is the effect of the d-tubocurarine on the results, a point raised by the authors themselves and not answerable without experiments in which another immobilization agent known to not affect heart rates unpredictably is used for comparison.

Still another uncertainty is the energy delivered to the heart by each pulse. The lack of such dose information in this and the other investigations cited renders it impossible to compare their findings except perhaps on a qualitative basis. Thus, the isolated-heart results of this investigation do not necessarily support or contradict those of Frey and Seifert (1968). However, the in-situ results do comprise evidence that RFR pulses synchronized with elements of the EKG (without or with delays) do not significantly affect in-vivo heart rates, a conclusion reached by Chou et al. (1980b) for intact rabbits exposed to 10-microsecond pulses of 2.45-GHz RFR at a pulse power density of 13.7 W/sq cm.

REFERENCES:
Chou, C.-K., L.F. Han, and A.W. Guy
MICROWAVE RADIATION AND HEART-BEAT RATE OF RABBITS
J. Microwave Power, Vol. 15, No. 2, pp. 87-93 (1980b)

Frey, A.H. and E. Seifert
PULSE MODULATED UHF ENERGY ILLUMINATION OF THE HEART ASSOCIATED WITH CHANGE IN HEART RATE
Life Sci., Vol. 7, No. 10, Part II, pp. 505-512 (1968)

exposure period, the R wave of each EKG was used as a trigger to deliver the RFR pulse on the rising phase of the R wave near its peak, so as to provide positive feedback. The duration of each R-R interval during periods I, II, and III was recorded as the primary datum, and the values for each heart were averaged over each 100 beats/period and presented as the mean duration and standard deviation (SD) thereof, in ms/beat. The results for 10.0 and 1.42 GHz were exhibited respectively in Tables 2 and 3 of the paper. (The nominal mean value was about 1000 ms/beat, or 1 beat/s.)

These results for in-situ exposure showed that the variations of means among the hearts were much larger than the period-to-period variations for each heart. The authors presented no statistical data but indicated that analysis of the results by the Wilcoxon matched-pairs, signed-rank test yielded no significant difference between the heart rates during the periods of RFR and no RFR. They also stated that analysis with a more powerful parametric two-tailed test showed no significant differences at the 5% level except for 3 of the 15 hearts in each table. (The latter point was verified by the reviewer by use of the t-test on the means and SDs in each table.)

In one of two sets of experiments with isolated hearts (10), each R wave was used to trigger a 100-microsecond pulse of 1.42-GHz RFR without delay, and the datum collected was the R-R interval. In the other set (6 hearts), each P wave was used to trigger an RFR pulse with a delay of 200-250 milliseconds, thus coinciding with the rising phase of the R wave. Except for the pulse duration, the latter procedure was analogous to that of Frey and Seifert (1968), who used 10-microsecond pulses. The primary datum collected was the P-P interval. In both sets, protocol 1 was used (RFR triggered only during period II).

The results were displayed in Tables 4 and 5 of the paper, respectively. These tables showed monotonic increases (found significant with the t-test by the reviewer) in the mean interbeat intervals for periods I, II, and III of all 16 hearts (apparent bradycardia). However, the authors stated: "For isolated hearts, the data showed that the heart rate was drifting throughout the experiment as it did in many unirradiated controls. If one compares the average of the mean of the two periods of no irradiation (I and III) with the mean of the irradiated period (II) and analyzes them by a parametric two-tailed test, it is apparent that the difference between the nonirradiated and the irradiated periods is not significant at the 5% level." The latter point was verified by the reviewer with the t-test.

The authors concluded: "Our experiments, like those of Kaplan et al. (1971) failed to demonstrate any microwave-induced change in heart rate. Hence we must hypothesize either (a) that the observations of Frey and Seifert (1968) and their predecessors were artifactual or (b) that our experimental procedure was sufficiently different to suppress the effect." They rejected hypothesis (a) and discussed several of the differences in experimental procedures that might account for the differences in findings.

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Liu, L.M., F.J. Rosenbaum, and W.F. Pickard
THE INSENSITIVITY OF FROG HEART RATE TO PULSE MODULATED MICROWAVE ENERGY

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AUTHOR ABSTRACT: Frey and Seifert (1968) have reported that pulse
modulated microwave irradiation of low average energy density can
produce tachycardia in isolated frog hearts. In an effort to examine
this phenomenon, two types of experiments were carried out: 1. frog
hearts were irradiated IN SITU with 100 microsecond bursts of microwave
energy at either 10.0 GHz or 1.42 GHz; 2. isolated frog hearts were
irradiated with 100 microsecond bursts of microwave energy at 1.42 GHz.
No significant changes in heart rate were observed.

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Study Type: Cardiovascular Effects, Biorhythms, Multiagent
Interactions; IN VIVO, IN VITRO; FROG
Effect Type: Bradycardia or tachycardia induced by exposure to pulsed
RFR of hearts in situ or isolated
Frequency: 1.42 or 10.0 GHz for in-situ exposure; 1.42 GHz for exposure
of isolated hearts
Modulation: 100-microsecond pulses delivered either on the rising phase
of the EKG R wave near its peak or triggered by the P wave and delivered
after a delay of 200-250 ms; at 1 beat/s, duty cycle was 0.0001
Power Density: Not determined; net (forward minus reflected) peak
powers were 160 mW in situ and 70 mW to isolated hearts at 1.42 GHz, and
122 mW in situ at 10.0 GHz
SAR: Not determined

EXPOSURE CONDITIONS: For in-situ exposure, each frog was immobilized
by subcutaneous injection with d-tubocurarine, its thorax was opened,
and a coaxial probe 3.58 mm in diameter was lightly pressed against the
sinus venosus of the heart. Two small alligator clips, one on the right
side of the neck and the other on the left thigh, served as EKG
electrodes. For exposure of an isolated heart removed from an
immobilized frog, the heart was placed ventral side up on two parallel
stainless-steel needles (used as EKG electrodes) at the bottom of a
plastic case and with the sinus venosus against a 1-mm-thick Lucite
window in the side of the case. The case was filled with frog Ringer's
solution. The coaxial probe was pressed lightly against the outside of
the window without any resistive connection to the heart.

Two protocols of EKG measurements during three successive periods (I,
II, III) of 100 heart beats each were used: 1) RFR triggered only during
period II and 2) RFR triggered during periods I and III but not II.

OTHER INFORMATION: In-situ heart exposures were performed on 15 frogs
each at 1.42 and 10.0 GHz. Protocol 1 was used on 8 hearts and protocol
2 on the other 7 hearts at each frequency. During each 100-beat

CLAPMAN
CAIN

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BIORHYTHM
CARDIOVASCULAR
EKG
FROG
IN-VITRO
PULSED
RFR

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1975
1400-3000
0-0.001
0-5.5
0

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2) The EKG waveforms presented in Fig. 4 were unusual. Did the authors correctly identify the components thereof? Specifically, they identified the prominent negative pulse in the unstimulated-heart example (Fig. 4a) as the P wave. If that were the case, then the components of the EKG associated with the QRS complex and the T wave would have unlikely shapes. (The authors stated that they had performed preliminary experiments to measure intracellular potentials from cardiac atrial cells to ensure correct identification of the P wave, but they presented no results of these experiments.) Instead, this pulse appears to be the QRS complex resulting from depolarization of the ventricular myocardium. The P wave normally would be the smaller biphasic wave preceding the monophasic pulse, and the T wave would be the slower positive peak midway between the large negative peaks.

3) When the heart was stimulated with 25-mA current pulses (Fig. 4b), the large negative pulse appeared to have changed to a positive pulse (were the recording leads reversed?), and the heart rate apparently doubled. If it is assumed, as above, that the (now) positive pulse is actually the QRS complex, then the trace shows that a large number of extrasystoles had occurred. Another questionable point is that although the authors supposedly had applied current pulses with 200-ms delays relative to the P wave, no regular 200-ms intervals between components were evident in Fig. 4b (using the time scale displayed).

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PULSE MODULATED UHF ENERGY ILLUMINATION OF THE HEART ASSOCIATED WITH CHANGE IN HEART RATE
Life Sci., Vol. 7, No. 10, Part II, pp. 505-512 (1968)

Liu, L.M., F.J. Rosenbaum, and W.F. Pickard
THE INSENSITIVITY OF FROG HEART RATE TO PULSE MODULATED MICROWAVE ENERGY
J. Microwave Power, Vol. 11, No. 3, pp. 225-232 (1976)

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Eight hearts were stimulated with 10-microsecond current unipolar pulses in the range from 1 microampere to 100 milliamperes (from a Grass S9 stimulator in series with a large resistance) instead of RFR. For this purpose, two additional platinum electrodes were mounted on either the ventral or dorsal side of the ventricle, and the EKGs were recorded with the electrodes used previously. The current pulses were triggered at delays of 0, 100, or 200 ms relative to the peak of the P wave, or at the initial rise of the QRS complex (paradigms similar to those for Groups 1-4).

Ventral stimulation with one polarity (current flow toward the bottom of the ventricle) yielded statistically significant heart-rate changes (increases) only with pulses that were delayed 200-300 ms after the P-wave peak and that had amplitudes in a "window" between 20 and 30 mA. (Larger or smaller pulses had no effect.) No numerical data were given, but a representative example of the effect was presented in Fig. 4, which showed two segments of an EKG each about 20 seconds in duration, one in the absence of stimulation and one for stimulation with 25-mA pulses delayed 200 ms. Based on the two-second time bar on the figure and the periodicity of the P wave, the unstimulated rate was about 30 beats/min, and the stimulated rate was about 60 beats/min and was accompanied by one or more pulses between successive P pulses but of opposite polarity and of about the same amplitude as the P wave.

The results for dorsal stimulation were similar except that the window was 50-60 mA. No effects were obtained for stimulation with pulses of the reverse polarity.

CRITIQUE: Although the RFR results of this investigation appear to be unequivocal, the absence of statistical data in the paper, not only for the hearts exposed to RFR but also for the control hearts, diminishes the degree of confidence in the negative findings obtained. For example, presentation of mean beat rates and standard errors for each group would have provided at least a semiquantitative measure of reliability to the reader.

Nevertheless, the negative findings obtained with more than 300 hearts, especially the results for Group 14, do not support the observation of tachycardia in isolated frog hearts exposed to RFR pulses 200 ms after the peak of the P wave reported by Frey and Seifert (1968). Moreover, Liu et al. (1976), in another endeavor to repeat the work of Frey and Seifert (1968), obtained negative results not only with isolated frog hearts, but also with frog hearts exposed in situ by opening the thorax.

The results for heart stimulation with current pulses were not presented in sufficient detail to evaluate in depth. Among the questions that can be raised, however, are the following:

1) For the example presented, the heart rate in the absence of the current pulses was only about 30 beats/min, which is about half the mean rate for the controls (Group 15) used in conjunction with the RFR experiments. Was this a "non-normal" heart?

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cm pulse power density. Those of Group 1 (20 hearts) were exposed in synchrony with the peak of the P wave of the EKG. Groups 2 and 3 (20 and 26 hearts) were exposed after delays of 100 and 200 ms, respectively. The hearts (20) of Group 4 were exposed in synchrony with the initial rise of the QRS complex of the EKG. Those of Group 5 (20) were exposed to unsynchronized 2-microsecond pulses at 500 pps (average power density of 5.5 mW/sq cm); in addition to determining the heart rates of this group, their temperatures were measured immediately before and after the 1 min of RFR exposure with a retractable thermocouple. No significant temperature changes were obtained. (It should be noted that Groups 4 and 5 were interchanged in Table 1 of the paper, but without consequences.)

Groups 6-8 (15 hearts each) were treated like those of Groups 1-3, but with 10-microsecond pulses. Groups 9-11 (15, 15, and 20 hearts) were also treated like Groups 1-3, but with 150-microsecond pulses of 1.4-GHz RFR at a pulse power density of 60 mW/sq cm. Groups 12-14 (15, 20, and 25 hearts) were treated with 10-microsecond pulses of 1.4-GHz RFR at 60 mW/sq cm (i.e., like Groups 9-11 except for the pulse duration), RFR values that were the same as those used by Frey and Seifert (1968).

The numbers of beats during the 1 min each before, during, and after exposure, denoted Rb, Rd, and Ra, respectively, were noted for each heart, and the minute-to-minute changes Rd-Rb and Ra-Rd were calculated. These calculations were also done for control Group 15 (43 hearts). The data were statistically analyzed with the Wilcoxon test by comparing all Rd-Rb values of each RFR-exposed group with all Rd-Rb values of the control group, and similarly for the Ra-Rd values. The small differences in the changes of heart rate between each RFR-exposed group and the control group were nonsignificant ($p > 0.05$), i.e., no significant bradycardia or tachycardia was induced by any of the RFR treatments used.

The statistical data leading to the finding above were not presented. However, as a representative example, the numbers of hearts that exhibited each (positive and negative) value of the changes Rd-Rb and Ra-Rd were displayed in bar-graph form for Group 14 (comparable to the 200-ms-delay group of Frey and Seifert) in Fig. 3 of the paper. (The values of Rb, Rd, and Ra were not given.) The results for Rd-Rb were that 24% of the hearts (the largest percentage) showed zero (no changes), 12% showed an increase of 2 beats (the largest increase observed), and 4% (1 heart) showed a decrease of 6 beats (the largest decrease observed); intermediate numbers of hearts and changes were obtained for the remaining 60%. For Ra-Rd, 28% of the hearts (the largest percentage) exhibited a decrease of 2 beats, 4% an increase of 2 beats (the largest increase), and 4% a decrease of 6 beats (the largest decrease). The results for the control group, also shown in Fig. 3, were basically similar. In addition, the mean values of Rb, Rd, and Ra for the control group were reported to be 58, 56, and 53 beats, respectively.

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AUTHOR ABSTRACT: Isolated frog hearts were irradiated with pulse
modulated microwave energy synchronized with the ECG. No statistically
significant or otherwise observable differences were found between the
heart rate of irradiated groups and the non-irradiated control group.
Experiments were performed to explore the possible effects of currents
induced between the recording electrodes. Increases in heart rate
occurred when applied current pulses between 20 and 30 mA were
synchronized with the ECG during an interval from 200 msec to 300 msec
after the peak of the P wave.

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Study Type: Cardiovascular Effects, Biorhythms; IN VITRO; FROG
Effect Type: Bradycardia or tachycardia induced in isolated hearts by
pulsed RFR triggered by the P wave of the EKG without and with delays
Frequency: 1.42 or 3 GHz
Modulation: Triggered 2- or 10-microsecond, 3-GHz pulses; triggered 10-
or 150-microsecond, 1.42-GHz pulses; untriggered 2-microsecond, 3-GHz
pulses at 500 pps (0.001 duty)
Power Density: 5.5 W/sq cm Pk at 3 GHz or 60 mW/sq cm Pk at 1.42 GHz
triggered; 5.5 W/sq cm Pk, 5.5 mW/sq cm Av at 3 GHz untriggered
SAR: Not measured

EXPOSURE CONDITIONS: Each isolated heart on a Lucite mount was
moistened with frog Ringer's solution and exposed within an anechoic
chamber to RFR for 1 min, preceded and followed by 1-min periods of no
exposure. The long axis of the heart was parallel to the E vector. Two
platinum wire electrodes, 0.25 mm in diameter, 1 mm above the Lucite
surface and disposed in a plane perpendicular to the E vector, were used
to measure EKGs during the 3-min test interval.

OTHER INFORMATION: The primary objectives of this study were to repeat
and extend the work of Frey and Seifert (1968) and determine the effects
of synchronized electric-current pulses on heart rate. Fourteen groups
of hearts were exposed to RFR. A fifteenth group that was sham-exposed
during the entire 3-min test interval served as controls. Still another
group was used for studying the effects of electric-current stimulation.

After decapitation of the frog, the heart was removed, washed for 10 min
in frog Ringer's solution, and monitored for beat rate. Hearts showing
irregular beat patterns were discarded. Most hearts were able to
maintain a regular, slowly decreasing beat rate for at least 20 min.

Groups 1-5 were exposed to 2-microsecond pulses of 3-GHz RFR at 5.5 W/sq

APPENDIX A

TEXTS OF ANALYSES COMPLETED DURING THE FIFTH PERIOD

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Tinney, C.E., J.L. Lords, and C.H. Durney
RATE EFFECTS IN ISOLATED TURTLE HEARTS INDUCED BY MICROWAVE IRRADIATION
IEEE Trans. Microwave Theory and Tech., Vol. 24, No. 1, pp. 18-24 (1976)

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AUTHOR ABSTRACT: Microwave irradiation at 960-MHz CW of isolated
poikilothermic hearts in Ringer's solution causes bradycardia.
Tachycardia is usually produced by generalized heating, suggesting the
possibility of a different mechanism in this case. The effect occurs
only over a narrow power range of approximately 2-10 mW/g absorbed by
the heart. It is hypothesized that microwave radiation causes
neurotransmitter release either by excitation of the nerve remnants in
the heart, or by some other mechanism, producing bradycardia over a
restricted range of power absorption.

Drugs which can change the response of the heart to transmitter
substances have been used, and the results support a neurotransmitter
release hypothesis. A generalized heating effect, causing tachycardia,
is predominant at higher levels of absorbed power.

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Study Type: Cardiovascular Effects, Biorhythms, Multiagent
Interactions; IN VITRO; TURTLE
Effect Type: RFR-induced tachycardia or bradycardia and alterations of
such effects by autonomic-nervous-system blocking agents
Frequency: 960 MHz
Modulation: CW
Power Density: Not measured
SAR: 8 W/kg

EXPOSURE CONDITIONS: The excised heart was placed in a petri plate, and
flexible plastic tubes filled with an agar-KCl solution to serve as
electrodes were sutured to the apex and aorta. The aorta suture was
also used to attach the heart to a strain gauge. The heart was immersed
in a bath of modified Ringer's solution, placed between parallel plates
3 cm apart, and allowed to stabilize for at least 40 min. The bath was
surrounded by a water jacket held at 12 deg C. Exposures to RFR were at
8 W/kg for 30 min. The EKG and the force of contraction were recorded
continuously during stabilization, exposure, and a 90-min or 30-min
postexposure period.

OTHER INFORMATION: This study was an extension of a previous one (Lords
et al., 1973) in which exposure of excised turtle hearts to 960-MHz CW
RFR caused bradycardia at SARs of 2-10 W/kg and tachycardia at 16-40
W/kg. They had hypothesized that RFR causes neurotransmitter release
by excitation of the remnants of the autonomic (parasympathetic and
sympathetic) nervous system. Under that hypothesis, exposure at SARs in
the lower range simultaneously stimulates the parasympathetic and
sympathetic systems, which yields bradycardia because the effects of

stimulation of the parasympathetic system usually predominate, and tachycardia is thermally induced at the higher SARs because the heart is poikilothermic. The present investigation was designed to test the neurotransmitter-release hypothesis by the use of release inhibitors.

The following is a brief description of the neural mechanism presented by the authors. A nerve ending consisting of an axon and a bouton is the stimulating part of the system, and a muscle fiber and receptor site make up the stimulated part of the system. In the sympathetic system, an action potential transmitted down the axon to the bouton causes the release of norepinephrine, which diffuses across the myoneural gap to the muscle receptor site and stimulates the muscle fiber. Thus, any stimulation of this system that causes an action potential to be transmitted down the axon, an increase in the sensitivity of the receptor site, release of preformed neurotransmitter, or a combination thereof, would increase the heart rate. The mechanism in the parasympathetic system is similar except that acetylcholine (ACh) is released, which slows the heart rate. The effect of the latter system is stronger than that of the former, so the net effect of simultaneous stimulation of both systems is bradycardia.

In experiment 1 with 16 control hearts (no RFR or neurotransmitter inhibitors used), the EKG and force of contraction were recorded for 120 min after preparation of the excised hearts. A least-squares fit of the heart rate vs time was performed for each heart, and the mean slope (rate of heart-rate change) and its standard deviation (SD) were calculated for the 16 hearts. The result for this group, presented in Table I of the paper, was a mean slope of $-0.0150 +/- 0.003$ beats/min. An average least-squares plot was displayed in Fig. 4, which showed that the initial mean heart rate was 20 beats/min.

In experiment 2 (8 hearts), the only treatment was exposure to RFR (at 8 W/kg). The EKG and force of contraction were recorded during the 40 min of stabilization, the exposure period, and 90 min after exposure. The average least-squares plot, exhibited in Fig. 5 of the paper, showed an initial rate of 20 beats/min and a slope of -0.0150 for the 40 min of stabilization as for the controls. However, the slope for the exposure period was $-0.1485 +/- 0.027$ (from Table I), indicating significant RFR-induced bradycardia. By t-test, the difference between this and the control slope was significant ($p<0.005$). (Figure 5 showed no line segment for the postexposure period.)

In experiment 3 (8 hearts), the only treatment given was addition of an optimal concentration (ascertained previously, as described below) of the parasympathetic-system inhibitor atropine sulfate to the Ringer's solution after the stabilization period. The results, presented in Fig. 7 of the paper, showed the -0.0150 control slope for the stabilization period, a slope of $+0.020 +/- 0.040$ (from Table I) during about the first 16 min after the addition of the blocker (indicative of tachycardia), and a compensatory negative slope for the next 14 min that brought the heart rate back to the original least-squares line. The probability level shown in Table I for the difference between the

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positive slope and the control slope was $p < 0.20$.

Experiment 4 (8 hearts) was similar to experiment 3, except that an optimal concentration of the sympathetic-system inhibitor propranolol hydrochloride (beta-blocker) was added after the stabilization period. The results, shown in Fig. 8, were approximately inverse to those with atropine, i.e., the slope was $-0.169 +/- 0.029$ ($p < 0.025$) for the first 9 min after the addition (indicative of more pronounced bradycardia than during the stabilization period), followed by a compensatory positive slope for the next 21 min that brought the heart rate back to the original least-squares line.

The optimal concentration of each inhibitor was determined by experiment (prior to experiments 3 and 4). The criterion stated by the authors was: "It was important to find a concentration which caused a definite change in rate, and at the same time allowed the heart to compensate for the drug over a short period of time (e.g., 20 min)." Satisfaction of this criterion meant that exposure of the heart to RFR after it compensated (returned to the original least-squares line) would avoid compounding the concurrent effects of the drug and the RFR. (The concentration selected for each was 0.016 microgram/ml.) By implication (not explicitly stated), after either inhibitor was added, its concentration was maintained for the remainder of the test period, so the return to the original least-squares line in experiments 3 and 4 occurred in the continued presence of the inhibitor.

In experiment 5 (8 hearts), atropine was added as before, and 30 min afterward, each heart was exposed to the RFR (8 W/kg) for 30 min, followed by a 30-min equilibration period. The results, presented in Fig. 1 of the paper, showed a least-squares plot that was similar to the one for atropine alone (Fig. 7) for the 70 min preceding RFR exposure, i.e., a slope of -0.0145 prior to the addition, the successive positive and compensatory negative slopes after the addition, and the return to the original least-squares line. From the onset of the RFR to the end of the equilibration period (60 min), the slope was $+0.1026 +/- 0.017$ (more pronounced tachycardia). By t-test, this slope was significantly higher ($p < 0.005$) than the $+0.020$ slope obtained with atropine alone (experiment 3). This result is opposite to the bradycardia obtained with RFR alone (slope of -0.1485 in experiment 2). The authors reasoned that blockage of the receptor sites of the parasympathetic system with atropine permitted the RFR to stimulate only the sympathetic system, thus yielding tachycardia.

Experiment 6 (8 hearts) was the same as experiment 5 except for the use of the beta blocker instead of atropine. As shown in Fig. 2 of the paper, the results prior to the onset of the RFR were again similar to those for the inhibitor alone (bradycardia followed by compensation), but the subsequent slope was $-0.2360 +/- 0.034$ ($p < 0.05$). With this slope, the heart rate decreased from about 19.5 beats/min at the onset of the RFR to less than 14 beats/min within 20 min of exposure. Again, the reasoning was that inhibition of the sympathetic system with the beta blocker allowed the parasympathetic system to have a greater

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bradycardial effect than the RFR alone (slope -0.1485, experiment 2).

In experiment 7 (6 hearts), a combination of both inhibitors (each at optimal concentration) was added to the Ringer's solution after the 40-min stabilization period. Twenty minutes later, the hearts were exposed to the RFR for 30 min. The authors stated: "Fig. 9 shows that when both of these drugs were used together, the effect was similar to that of the controls. Fig. 9 further shows that microwave irradiation of approximately 8 mW/ cu cm applied 20 min after the addition of both atropine and beta blocker caused little change in heart rate. This was to be expected since both types of receptor sites were blocked." (The results displayed in that figure showed that the slope was -0.007 for the stabilization period, +0.020 during the 20 min preceding RFR exposure, and +0.011 +/- 0.01 after the RFR was turned on.)

In experiment 8, the RFR was turned on after the stabilization period and the drugs were added after the first 10 min of the 30-min exposure. The results (Fig. 10 of the paper) were bradycardia during the 10 min of RFR only (similar to that obtained in experiment 2) followed by return to the initial least-squares line when the inhibitors were added. Thus, as stated by the authors, "...application of the drugs removes the microwave-induced bradycardia." (No numerical data were given.)

To determine the relation between temperature rise in the heart and SAR, a nonperturbing (liquid-crystal) thermometer was inserted into the aorta of an excised heart in place of the agar-KCl electrode, and measurements were made continuously for 130 min while input power levels of 50 to 1500 mW of 960-MHz CW RFR were applied. The authors did not present data on heart temperature rise vs input power. Instead, they showed a graph of power absorbed by the heart vs power to the irradiator (Fig. 12), which had a slope of about 8 mW per 100 mW. Thus, a representative heart of 1 cu-cm volume exposed at 100 mW would have an SAR of about 8 W/kg. (In their conclusion section, the authors mentioned that they found, in subsequent experiments, that the calibration of SAR vs input power was affected by changes of RFR losses in one of the components between the source and the parallel plates used for exposure, but that the SAR range for the effects observed, 2-10 W/kg, was not altered.)

CRITIQUE: There were several unclear aspects in this study. First, the figures exhibiting average least-squares plots of beat-rate vs time for the various experiments were displayed in idealized fashion, without any actual data. In the absence thereof, it seems unlikely that after the effect of either inhibitor had diminished in experiments 3 and 4, the mean heart rate would return precisely to the least-squares line obtained before treatment (as was shown in Figs. 7 and 8). Moreover, the statistical data presented in Table I, which provided the average slope and SD for the hearts of each experiment and the range (maximum and minimum) of correlation coefficients, did not permit analysis of the results in adequate detail.

Second, the description of the procedure used to supply the inhibitors to the heart did not include any details regarding maintenance of their

concentrations. As indicated in the previous section, it was surmised that once each inhibitor was added to the Ringer's solution, its concentration was held constant for the rest of the test period. If so, then the heart was able to compensate for the continuing presence of the inhibitor, but possible mechanisms for such compensation were not discussed. Would the results of subsequently exposing the heart to the RFR have been influenced by such compensation?

Third, as noted in the previous section, heart-rate data taken during the postexposure period of experiment 2, in which RFR was the sole treatment, were not presented. Did the RFR-induced bradycardia persist for a significant period after cessation of the RFR? In this context, it should be noted that the postexposure results of experiment 5, in which exposures were done after the addition of atropine, were presented and they imply the persistence of tachycardia for the entire 30-min postexposure period. On the other hand, the postexposure results of experiment 6, in which RFR exposure was done after adding the beta blocker, were also not presented.

Despite the uncertainties discussed above, the effects described by these authors do support their hypothesis that the observed effects of RFR on the beat rates of excised hearts were due to the release of neurotransmitters in the remnants of the autonomic nervous system. Qualitatively similar results were obtained by Reed et al. (1977) in isolated rat hearts treated with atropine and propranolol. However, in view of the absence of the rest of the autonomic nervous system and its regulatory functions, the relationship of such findings to possible cardiovascular effects of RFR on intact animals is unclear. Moreover, Chou et al. (1980b) exposed intact rabbits to 2.45-GHz CW RFR and found no significant effects on heart rate for power densities up to 80 mW/sq cm.

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Radio Sci., Vol. 12, No. 6S, pp. 161-165 (1977)

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TINNEY
LORDS
DURNEY

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BIORHYTHM
CARDIOVASCULAR
CW
DRUG-RFR
EKG
IN-VITRO
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Galvin, M.J., M.S. Dutton, and D.I. McRee
INFLUENCE OF 2.45-GHZ CW MICROWAVE RADIATION ON SPONTANEOUSLY BEATING
RAT ATRIA

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AUTHOR ABSTRACT: The chronotropic and inotropic effects of 2.45-GHz
continuous wave (CW) microwave radiation were investigated in the
isolated spontaneously beating rat atria. Isolated atria were placed in
specially designed tubes inserted into a waveguide exposure system. The
atria were then irradiated for a period of 30 min, followed by a 30-min
recovery period. The control atria were prepared simultaneously and
sham exposed. Experiments were conducted at two temperatures, 22 and 37
deg C, and two absorption rates, 2 mW/g and 10 mW/g.

At both temperatures the rate of atrial contraction was not altered by a
30-min exposure at either 2 or 10 mW/g. The average rate (beats per
min) was approximately 100 for both the control and exposed atria at 22
deg C and 215 beats per min for both the control and exposed atria at 37
deg C. In addition, no inotropic effects on the spontaneously beating
atria were noted at any exposure level. These data suggest that 2.45-
GHz CW microwave radiation at these intensities has no overt effect on
these variables in isolated rat atria.

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Study Type: Cardiovascular Effects, Biorhythms; IN VITRO; RAT
Effect Type: RFR-induced alterations of heart-beat rate or muscle-
contraction force
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not measured
SAR: 2 or 10 W/kg

EXPOSURE CONDITIONS: Isolated spontaneously beating atria from pairs of
rat hearts were suspended in glass tubes and continuously perfused with
aerated Krebs Henseleit solution in a common flow system. Both tubes
were inserted in a section of waveguide with their axes parallel to the
E vector. The waveguide section was filled with distilled water, and a
quarter-wave dielectric plate at the source end was used to match the
impedance of the section to that of air. The temperature of the water
was maintained at either 37 or 22 deg C. The tube containing the
specimen to be exposed was placed against the immersed surface of the
plate and the other (control) tube was located 9.5 cm from that surface,
thereby receiving essentially no RFR because of the attenuation by the
intervening water. Exposures were for 30 min, preceded and followed by
30 min each for equilibration and recovery.

OTHER INFORMATION: The description of the exposure system was derived
from Galvin et al. (1980b). SARs were determined from slopes of time-

temperature profiles produced by exposure of atria at high levels of RFR and measured with a nonperturbing temperature probe sutured to the upper atrium.

After decapitating each rat, the heart was removed and the atria were isolated and suspended in a glass tube with the upper end attached to a force-displacement transducer and the lower end to a glass rod with suture silk. The initial resting tension was adjusted to 600 mg.

Experiments were performed at SARs of 2 and 10 W/kg and water-bath temperatures of 37 and 22 deg C. Developed contractile force and beat rate of the exposed and control specimens were recorded continuously and sampled during the equilibration, exposure, and postexposure periods. The results for each combination of SAR and bath temperature were subjected to analysis of variance for 2 treatments (RFR vs control) and 10 sampling times (5 min before exposure, minutes 0, 5, 10, 15, 20, 25, and 30 of exposure, and minute 10 and 20 after exposure, for a total test period of 55 min). In addition, because the initial beat rates were different for the individual atrial preparations, the rates were expressed as percentages of the initial value and similarly analyzed. The mean values for each group (6 to 8 specimens per group) were presented graphically in both beats per min with standard-error (SE) bars and percentages (also with SE bars) vs time.

With 2 W/kg at 37 deg C, the mean beat rates for the RFR and control groups both averaged about 230 beats/min and differed from one another by no more than 2 beats/min at corresponding sampling times, with SEs of about +/- 10 beats/min. Also, the percentages of initial value were all between 98% and 100%, with SEs not exceeding +/- 3%. Thus, none of the differences between these two groups was statistically significant.

With 10 W/kg at 37 deg C, the mean beat rates for the RFR and control groups both averaged 215 beats/min, but the variations in mean beat rate and in percentage of initial rate for the RFR group during the exposure period were larger than at 2 W/kg. However, the authors indicated that the differences between the RFR and control groups at 10 W/kg were not significant. They also stated (without presenting data) that the average developed tension was 640 mg and was not influenced by RFR exposure at either SAR.

The results with 2 or 10 W/kg at 22 deg C showed much lower beat rates, i.e., 102 and 106 beats/min, respectively, but again there were no significant differences between exposed and control groups at either SAR. The average tension at this temperature was 1200 mg and was not affected by RFR exposure (no data presented).

CRITIQUE: Although the authors had not presented the numerical results of their analyses of variance, their finding of no RFR effect in the experiment with 2 W/kg at 37 deg C was clearly supported by the graphical data exhibited (in Fig. 3 of the paper). However, in the graphs for the experiment with 10 W/kg at 37 deg C (Fig. 4 of the paper), there appeared to be a downward trend in mean beat rate for the

RFR group during the interval from minute 5 to minute 25 of the exposure period. The mean value at minute 5 was 223 beats/min and it decreased monotonically to 211 beats/min at minute 25. A smaller downward but nonmonotonic trend was discernible for the control group, i.e., 216 and 213 beats/min respectively at minutes 5 and 25. Thus, the mean rate for the RFR group was 7 beats/min higher at minute 5, and 2 beats/min lower at minute 25, than for the control group, with a crossover at about minute 15. In the graphs of percentages of initial rates, the downward trend was still evident for the RFR group but not the control group. However, the reviewer applied the t-test to the largest difference between the groups (at minute 5) and found it to be nonsignificant ($p > 0.05$), thus supporting the authors' finding of no RFR effect for this case as well.

The negative results of this investigation with isolated rat-heart atria are at variance with those of Tinney et al. (1976) with isolated turtle hearts and Reed et al. (1977) with isolated rat hearts, who reported the occurrence of bradycardia at comparable SARs and ascribed the effect to RFR stimulation of the remnants of the sympathetic and parasympathetic nervous systems. The reasons for such differences are speculative.

In view of the absence of the rest of the autonomic nervous system and its regulatory functions in all of those investigations, the relevance of the findings (positive or negative) to possible cardiovascular effects of RFR on intact animals is unclear. Regarding the latter, Galvin and McRee (1981a) found that in-vivo exposure of normal and ischemic cats to 2.45-GHz CW RFR at 30 W/kg had no influence on the myocardium or its neural components. Also, Chou et al. (1980b) found no significant effects on heart rate in intact rabbits exposed to 2.45-GHz CW RFR at SARs in the heart up to about 5 W/kg (power densities up to 80 mW/sq cm).

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Radio Sci., Vol. 12, No. 6S, pp. 161-165 (1977)

Tinney, C.E., J.L. Lords, and C.H. Durney
RATE EFFECTS IN ISOLATED TURTLE HEARTS INDUCED BY MICROWAVE IRRADIATION
IEEE Trans. Microwave Theory and Tech., Vol. 24, No. 1, pp. 18-24 (1976)

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Reed, J.R.III, J.L. Lords, and C.H. Durney
MICROWAVE IRRADIATION OF THE ISOLATED RAT HEART AFTER TREATMENT WITH ANS
BLOCKING AGENTS
Radio Sci., Vol. 12, No. 6S, pp. 161-165 (1977)

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AUTHOR ABSTRACT: Microwave irradiation (960-MHz CW) at a specific
absorption rate (SAR) near 1.5 W/kg induced bradycardia in isolated rat
heart as reported earlier. When parasympathetic and sympathetic nerves
were simultaneously blocked, respectively, by atropine and by
propranolol, no significant effect of irradiation was observed.
Previous experiments have revealed that atropine plus irradiation
produces tachycardia and propranolol plus irradiation produces
bradycardia. The results may indicate a microwave neuron or microwave-
synapse interaction by a mechanism other than generalized heating of
tissues.

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Study Type: Cardiovascular Effects, Biorhythms, Multiagent
Interactions; IN VITRO; RAT
Effect Type: Suppression of RFR-induced bradycardia and tachycardia by
autonomic-nervous-system blocking agents
Frequency: 960 MHz
Modulation: CW
Power Density: Not Measured
SAR: 1.5-2.5 W/kg

EXPOSURE CONDITIONS: Each freshly excised rat heart was allowed to
stabilize for 10-20 min, during which it was back-perfused with Ringer's
solution. The heart was then perfused for 10 min with Ringer's solution
containing 0.5 microgram/ml of atropine, after which it was perfused
with Ringer's solution containing 0.5 microgram/ml each of atropine and
propranolol, presumably for the remainder of the test period, which
totaled 90 min. After 30 to 40 min of elapsed time, the heart was
exposed for 10 min of RFR between parallel plates within a Faraday cage.
Each exposed heart was paired with a control heart for evaluation.
Heart contractions were monitored with a strain gauge.

OTHER INFORMATION: The SAR was determined at the end of each experiment
from the thermal curve obtained by exposing the heart with a tenfold
higher intensity for 30-second periods while its temperature increase
was measured with a nonperturbing probe (no data presented).

The results of a pair of hearts not perfused with blocking agents were
exhibited in Fig. 1 of the paper for the period from min -5 to min +15
relative to the start of RFR- or sham exposure. The control heart
displayed a stable but slightly bradycardial rate, from 15 beats per min
at min -5 to 14 beats per min at min +15. However, the rate for the
RFR-exposed heart was higher initially and less stable; it rose from

about 17.5 beats per min at min -5 to 19 beats per min at about min -1, decreased roughly linearly during exposure to 14 beats per min (about the same rate as the control heart) by about min +11, and rose again at min +14.

The results for a pair of hearts administered the blocking agents were similarly displayed in Fig. 2. Both hearts exhibited slight bradycardia with about the same slope during the stated period, but with different initial rates (about 15 and 12 beats per min for the sham- and RFR-exposed hearts, respectively).

The averaged slopes for 6 pairs of hearts perfused with the blocking agents were shown in Fig. 3 of the paper for the 5-min interval prior to exposure, the 10 min of exposure, and the 5-min interval after exposure. (No actual data were presented.) For the preexposure interval, the mean slopes for the 2 groups were both negative (bradycardia) and almost the same value. During the exposure interval, the slope for the RFR group was the same as before, but the slope for the control group was less negative. However, compensation for this difference was evident for the 5-min postexposure period, during which the slopes for both groups were positive, but that of the RFR group was somewhat steeper; at min +15, the mean beat rate for the RFR group was less than 1 beat per min lower than for the sham group. Also displayed in Fig. 3 were the standard-deviation (SD) bars for these groups at minutes -5, +10, and +15. The differences in mean beat rate between the groups at corresponding times were less than 1 SD.

The mean slopes (time rates of change of heart-beat rate and the SDs thereof, in beats/min per min) for the preexposure, exposure, and postexposure intervals for all four groups were summarized in Table 1 of the paper. The values for Group 1 (6 hearts administered the blockers and sham-exposed) were -0.229 +/- 0.279, -0.114 +/- 0.131, and +0.007 +/- 0.188, respectively. For comparison, the corresponding values for Group 2 (6 hearts administered the blockers and RFR-exposed) were -0.225 +/- 0.339, -0.242 +/- 0.205, and +0.119 +/- 0.319. Similarly, the values for Group 3 (3 hearts not given the blockers prior to sham exposure) were -0.067 +/- 0.480, -0.018 +/- 0.063, and -0.069 +/- 0.223 for the preexposure, exposure, and postexposure intervals, respectively. For comparison, the corresponding values for Group 4 (4 hearts not given the blockers prior to RFR exposure) were -0.42 +/- 0.172, -0.914 +/- 1.47, and +1.15 +/- 2.51, with a footnote that the last two SDs "greatly increased due to extreme bradycardia in 2 of 4 experiments," and that "all preparations exhibited significant bradycardia."

CRITIQUE: The rationale for the sequential perfusion of the heart with atropine alone and the atropine-propranolol mixture is unclear. The authors stated that "This sequence allowed observation of the effect of each drug as it was added..." but they presented no data for such effects. In fact, they did not provide any results for times earlier than 5 min before RFR- or sham exposure or for times later than about 15 min after RFR- or sham exposure.

The only actual data given on heart-beat rate vs time were those in
Figs. 1 and 2. Figure 1 was for a pair of hearts not administered the
drugs; the heart that was RFR-exposed showed a larger bradycardial
effect during the exposure interval than the sham-exposed heart. By
contrast, the results in Fig. 2 for the pair of hearts given the drugs
showed no difference in bradycardia between the RFR- and sham-exposed
hearts. Thus, it could be concluded that the RFR stimulated the
remnants of the autonomic system in the former experiment and that the
blockers rendered the RFR ineffective in the latter experiment.
However, the validity of this finding is diminished by the observation
that the beat rates for the RFR-exposed hearts in both experiments were
less stable that the sham-exposed hearts throughout the experiment
(including the preexposure interval), an indication of the presence of
uncontrolled non-RFR factors.

The averaged slopes presented in Fig. 3 and Table 1 do not provide
greater credence to the finding either, since use of the t-test on the
means and SDs cited above showed that the differences between groups for
corresponding time intervals were nonsignificant ($p > 0.05$) and that the
time variations for each group were also nonsignificant. Use of larger
numbers of hearts in each experiment might have yielded results of
greater statistical validity.

Qualitatively similar findings were obtained by Tinney et al. (1976) in
isolated turtle hearts treated with atropine alone, propranolol alone,
and a mixture of the two. However, in view of the absence of the rest
of the autonomic nervous system and its regulatory functions, the
relationship of such findings to possible cardiovascular effects of RFR
on intact animals is unclear. Moreover, Chou et al. (1980b) exposed
intact rabbits to 2.45-GHz CW RFR and found no significant effects on
heart rate in intact rabbits exposed to 2.45-GHz CW RFR at SARs in the
heart up to about 5 W/kg (power densities up to 80 mW/sq cm).

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MICROWAVE RADIATION AND HEART-BEAT RATE OF RABBITS
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Tinney, C.E., J.L. Lords, and C.H. Durney
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IEEE Trans. Microwave Theory and Tech., Vol. 24, No. 1, pp. 18-24 (1976)

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increase in percentage of deaths with increasing dose for both the RFR
and sham groups. This was also true for the percentage of cataleptic
responses for the sham group. However, the dependence on dose in the
corresponding results for the RFR group was not clear. Instead, the
change in percentage of responses with increasing dose was not
monotonic. Also, the percentage for the RFR group at 10 mg/kg was
higher than for the sham group, but lower at 15 and 20 mg/kg.

Lacking in this investigation were data on control animals administered
saline instead of the drugs. Such data might have more clearly
delineated subtle non-RFR factors that may have influenced the results.

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EFFECTS OF ETHANOL ON CENTRAL DOPAMINE FUNCTIONS
Life Sci., Vol. 27, No. 4, pp. 299-304 (1980)

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have dissipated in some rats."

Presumably the results for the animals that did not exhibit the effect
were included in the statistical treatment of the data. The last
sentence in the quotation above suggests that perhaps exposure to RFR
after drug administration would yield more definitive results.

It is interesting to note that the mean colonic temperatures of the
apomorphine-injected and amphetamine-injected groups immediately after
exposure to RFR were both 0.1 deg C higher than for their respective
sham-exposed groups (38.3 vs 38.2 deg C in both cases). Presumably
the temperatures of the RFR group were even higher during exposure, and
the postexposure difference between the RFR and sham groups was due to
the residual thermal response to the RFR.

In the light of the foregoing point, not clear was the influence of
thermoregulation on the results. For both drugs, the differences in
mean colonic temperature between RFR and sham groups during the
postinjection intervals were smaller than the changes per se. With
apomorphine, for example, adding the mean colonic temperature of the RFR
and sham groups before injection to the maximum changes thereof (15 min
after injection) yielded actual temperatures of 37.35 and 37.57 deg C,
respectively, a difference of only 0.22 deg C. Was this difference
statistically significant? Would similar results be obtained if the
preinjection colonic temperatures of rats were raised by a means other
than RFR?

In speculating on possible mechanisms for their positive results, the
authors noted that "...since albino rats were used in our experiments
and albino animals have been shown to have aberrant metabolic and
neurological functions (Creel, 1980), it may be interesting to repeat
some of these experiments using hooded rats, eg, Long-Evans."

The peak power density of the RFR pulses was at least 1 W/sq cm, within
the range of perception of the pulses as sound. Thus, it is possible
that the rats perceived the pulses and were stressed thereby, and that
the stress may have persisted well into the postexposure period.

The results on the effects of RFR on apomorphine-induced stereotypic
behavior appear to be somewhat ambiguous because the percentage scores
for the RFR group were lower than for the sham group for two of the
responses (1 and 3) and higher for two of the other responses (4 and 5).
Evidently the authors gave qualitatively greater weight to responses 4
and 5 than to 1 and 3, a reasonable point.

Regarding the stereotypic-behavioral results for amphetamine (in which
all six behavioral responses were given equal weight), although the
differences between the RFR and sham groups were nonsignificant, it is
interesting that the sham group (as well as the RFR group) exhibited a
high score for "head sway," one of the "abnormal" responses.

The results on morphine-induced lethality indicated a clearly monotonic

each was determined for each rat. Application of the 2-tailed Mann-Whitney U-test to the averaged scores for each of the six behaviors (displayed in Table 1 of the paper for 12 RFR-exposed and 12 sham-exposed rats) yielded nonsignificant (p>0.05) differences between the groups.

The effect of RFR on amphetamine-induced hyperthermia was also studied. Colonic temperatures of rats were measured immediately after exposure and at 15-min intervals during the 90-min period after the rats were injected i.p. with amphetamine (5 mg/kg). The results were displayed in Fig. 3 as the change in mean colonic temperature for each group vs time after injection. The caption indicated that the mean temperature at zero time was 38.3 +/- 0.1 deg C for the RFR group (20 rats) and 38.2 +/- 0.1 deg C for the sham group (20 rats). The mean temperature of the sham group reached its maximum at 45 min, at which time it had increased by 1.4 deg C to a maximum of 39.6 deg C, and it diminished to about 39.3 deg C at the end of the 90-min period. By contrast, the temperature of the RFR group attained its maximum at 60 min, at which time it had increased by 1.2 deg C to 39.5 deg C, and it diminished to 39.2 deg C at 90 min. The differences in temperature increases for the two groups were significant (p<0.02).

In the final experiment, morphine sulphate was injected i.p. into rats at doses of 1, 5, 10, 15, or 20 mg/kg immediately after exposure. The number of animals exhibiting catalepsy at 30 min after injection, i.e., general muscular rigidity and a certain posture for more than 1 min, was recorded. Also recorded was the number of rats that died within 2 hr after injection.

The percentages of RFR- and sham-exposed rats that exhibited catalepsy for each dose were displayed in Fig. 4. For the sham-exposed rats, the mean values for doses 1, 5, 10, 15, and 20 mg/kg and the numbers of rats (in parentheses) were 0% (6), 0% (6), 36% (30), 50% (18), and 78% (18), respectively. The corresponding values for the RFR-exposed rats were 0% (6), 33% (6), 57% (32), 33% (18), and 53% (17). The authors indicated that the differences were significant (p<0.05) by use of the chi-square test. The percentages of deaths for those rats within 2 hr were similarly displayed in Fig. 5. There were no deaths in either group for doses of 1 or 5 mg/kg. For doses of 10, 15, and 20 mg/kg, the values for the sham-exposed rats were about 16%, 33%, and 67%, respectively, and the corresponding values for the RFR-exposed rats were 37%, 44%, and 65%. These differences were also significant (p<0.02).

CRITIQUE: In their discussion, the authors stated: "It may also be important to point out that the effect of microwaves on drug action was not observed in all of the animals irradiated. About 70% of the irradiated rats showed positive responses. Therefore, large samples were required to achieve statistically significant differences in response between the microwave- and sham-irradiated animals. We are probably working at an intensity of microwave irradiation close to the threshold level. Furthermore, since in our experiments drug actions were studied after microwave irradiation, the effect of microwaves might

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subcutaneously injected immediately after exposure. Each rat was then placed in a plastic cage covered with a metal grid and its stereotypic behavior was observed 5 min after injection and at subsequent 15-min intervals for 1 hr, using the following scale: 1) awake but largely immobile; 2) moving with short bursts of sniffing; 3) moving over the area of the cage with continuous sniffing and rearing; 4) some or no movement and continuous sniffing with head directed down; 5) same as 4, but with licking, biting, or gnawing. The sum of the five ratings was taken as the stereotypic behavior score for the rat.

The results of the first experiment were a mean score of 17.2 for 15 RFR-exposed rats and 14.5 for 9 sham-exposed rats (no standard errors or deviations given). For each group, the percentage of the mean score in each rating was displayed in Fig. 1 of the paper. For the RFR group, the values were 8%, 11%, 32%, 28%, and 21% for ratings 1 through 5, respectively. The corresponding values for the sham group were 20%, 11%, 38%, 24%, and 7%. Thus, the RFR group showed lower percentages for ratings 1 and 3, and higher percentages for ratings 4 and 5, than the sham group. Based on use of the 2-tailed Mann-Whitney U-test, the differences were significant (p<0.02). The authors stated that: "Microwave exposure shifted the distribution towards the higher scores, ie, more intense stereotypy with biting and clawing being observed in the microwave-treated animals."

The effect of RFR exposure on apomorphine-induced hypothermia was studied in the next experiment. The colonic temperature of each rat was measured immediately after exposure, the rat was injected i.p. with apomorphine (1 mg/kg), and its colonic temperature was recorded for 1 hr at 15-min intervals. The results were displayed in Fig. 2 of the paper as the mean change in colonic temperature vs time interval after injection for 15 RFR-exposed rats, and similarly for 12 sham-exposed rats. As indicated in the caption, the mean colonic temperature and standard error (SE) immediately after exposure was 38.3 +/- 0.1 deg C for the RFR group and 38.2 +/- 0.2 deg C for the sham group.

Fifteen min after injection, the mean temperature of the RFR group had decreased by 0.95 +/- 0.07 deg C, whereas the decrease for the sham group was only 0.63 +/- 0.09 deg C. Progressive recovery from the hypothermia was evident for both groups at 30 min and 45 min after injection. By a nonparametric test (Krauth, 1980), the difference between the groups was significant (p<0.02), indicating that the RFR had enhanced the hypothermic effect of the apomorphine.

In the next experiment, the effect of RFR on the stereotypy syndrome induced by amphetamine was studied. Each rat was injected i.p. with d-amphetamine (sulphate, 10 mg/kg in saline) immediately after exposure, placed in a plastic cage, and observed for the presence of any of three normally occurring behaviors (immobility, rearing, and forward walking) and three abnormal behaviors (backward walking, circling, and head swaying). The rats were observed for 1 min every 5 min during a 1-hr session, starting 4 min after injection. The occurrence of each behavior was recorded on an all-or-none basis and the total incidence of

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Lai, H., A. Horita, C.-K. Chou, and A.W. Guy
PSYCHOACTIVE-DRUG RESPONSE IS AFFECTED BY ACUTE LOW-LEVEL MICROWAVE
IRRADIATION

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AUTHOR ABSTRACT: The effects of various psychoactive drugs were studied
in rats exposed for 45 min in a circularly polarized, pulsed microwave
field (2450 MHz; SAR 0.6 W/kg; 2-microsecond pulses, 500 pps).
Apomorphine-induced hypothermia and stereotypy were enhanced by
irradiation. Amphetamine-induced hyperthermia was attenuated while
stereotypy was unaffected. Morphine-induced catalepsy and lethality
were enhanced by irradiation at certain dosages of the drug. Since
these drugs have different modes of action on central neural mechanisms
and the effects of microwaves depend on the particular drug studied,
these results show the complex nature of the effect of microwave
irradiation on brain functions.

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Study Type: Nervous System, Multiagent Interactions, Behavior,
Physiology and Biochemistry; IN VIVO; RAT
Effect Type: RFR-induced alterations of the effects of psychoactive
drugs administered postexposure
Frequency: 2.45 GHz
Modulation: 2-microsecond pulses at 500 pps (0.001 duty cycle)
Power Density: 1 mW/sq cm Av (circular polarization); 3-6 mW/sq cm
(equivalent linear polarization)
SAR: 0.6 W/kg

EXPOSURE CONDITIONS: Rats were individually exposed to circularly
polarized 2.45-GHz pulsed RFR at a time- and spatially-averaged power
density of 1 mW/sq cm in a cylindrical-waveguide system (Guy et al.,
1979) for 45 min at an ambient temperature of 22.0 +/- 0.1 (SEM) deg C
(range 21-24 deg C). Immediately after exposure, one of several drugs
was administered and the effects thereof were studied. Control rats
were sham-exposed concurrently and otherwise treated similarly. The
SAR, determined calorimetrically, was 0.6 W/kg. The corresponding power
density for linearly polarized plane-wave RFR would be 3 to 6 mW/sq cm.

OTHER INFORMATION: Male Sprague-Dawley rats (250-300 g) were used.
Each rat was given only one treatment. All drug experiments were
performed in the blind (without knowing whether any given rat was RFR-
or sham-exposed). The method used in assessing stereotypic behavior was
similar to that by Lai et al. (1980), in which the preinjection agent
was ethanol rather than RFR.

The first experiment was directed toward determining the effect of RFR
exposure on the stereotypy induced by apomorphine. Apomorphine (as
hydrochloride, 1 mg/kg, with 1 mg/ml of 1-ascorbic acid, in saline) was

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exposed for 6 months after parturition, and offspring were exposed without dams for 6 months more. In the second study, dams were exposed for 3 hr/day, 7 days/week, starting near the beginning of the first trimester of pregnancy, dyads were exposed for 6 months, and offspring were exposed for 3 additional months without their dams.

Presumably, Albert et al. had used monkeys from the second study (based on the statements that exposures were begun on the 35th day of gestation and that the offspring were exposed for 9.5 months from birth). The point is that organogenesis in the squirrel monkey is completed within the first trimester of pregnancy, during which the brain may be more sensitive to exogenous agents (such as RFR) than subsequently. However, perhaps the negative results of Albert et al. (1981b) render this point moot.

These negative results are at variance with those of another study by Albert et al. (1981a), in which the mean density of Purkinje cells in the cerebella of rats exposed prenatally to 2.45-GHz or 100-MHz RFR at whole-body SARs of about 2 W/kg was significantly lower than for sham-exposed rats. Albert et al. suggested that differences in species and in exposure methods, geometrical configurations of the head, and exposure protocols might account for the differences in findings. It is possible that local SARs in the brain of a rat may be higher than in the brain of a squirrel monkey at comparable whole-body SARs. However, in Albert et al. (1981a) and in a previous paper (Albert and DeSantis, 1975), the authors reported the absence of morphologic changes in Purkinje cells.

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Radio Sci., Vol. 17, No. 5S, pp. 135-144 (1982)

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thick boxes of Styrofoam. The temperature rises in the 2 dolls were measured after concurrent exposure in a module to specified values of input power and duration.

One of the dolls was also exposed to far-field 2.45-GHz RFR, with face toward the source and long axis parallel to the E vector, in an anechoic chamber at specified power densities for appropriate durations, and the resulting temperature rises were used to calculate the input power to the module necessary to yield the same temperature rise as exposure at 10 mW/sq cm in the anechoic chamber (for the same duration). In this manner, it was found that an input power of 15 W yielded the equivalent of 10 mW/sq cm, and that the corresponding SAR was 3.4 W/kg per doll.

The development of the mammalian brain is dependent on migration of nerve cells, the patterns of which are well understood for the cerebellum. The cerebellar Purkinje cells were selected for study because they provide a relay station for major input to, and output from, the cerebellum and are readily identifiable in the interface between the molecular and granular layers.

Albert et al. had obtained 7 of the RFR-exposed and 7 of the sham-exposed offspring studied by Kaplan et al. (1982). These monkeys were weighed and anesthetized, and their brains were fixed with formalin by cardiac perfusion within 24 hr after receipt. The brains were removed and their weights and volumes were determined. The cerebella were dissected and the inferior vermis of each was separated and embedded in paraffin. The preparation was serially sectioned in the parasagittal plane at thicknesses of 10 micrometers and stained with hematoxylin-eosin. The uvula of the inferior vermis was selected for study because its mean cell density is representative of the mean cell density of the entire cerebellum.

The density of Purkinje cells in each uvula was estimated by determining the area of the Purkinje cell layer and counting the number of Purkinje cells therein by light microscopy, with the result expressed as the number of cells per sq mm. The linear density was also determined by counting the number of cells per mm in the interface between the molecular and granular regions of each section and averaging the results over the sections. Only cells that displayed a visible nucleolus were counted.

No significant differences between RFR- and sham-exposed groups were found in whole-body mass, brain mass, brain volume, or Purkinje-cell counts per sq mm or per mm.

CRITIQUE: It should be noted that Kaplan et al. had carried out two studies, the second of which was described briefly in a note added in proof to the description of the first study (Kaplan et al., 1982), and there may be some confusion regarding which animals were used by Albert et al. (1981b). In the first study, exposure of dams at 3.4 W/kg was started at a mean gestation age of 8.5 weeks, i.e., near the beginning of the second trimester of pregnancy, dyads of dam and offspring were

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Albert, E.N., M.F. Sherif, and N.J. Papadopoulos
EFFECT OF NONIONIZING RADIATION ON THE PURKINJE CELLS OF THE UVULA IN
SQUIRREL MONKEY CEREBELLUM
Bioelectromagnetics, Vol. 2, No. 3, pp. 241-246 (1981b)

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AUTHOR ABSTRACT: Pregnant squirrel monkeys were exposed to 2450-MHz
(CW) microwaves at an equivalent power density of 10 mW/sq cm (SAR 3.4
mW/g) for three hours daily in a cavity-cage module. The exposure began
when pregnancy was determined by a hormonal method, and continued
through the offspring's first 9.5 months. After irradiation, the brains
of the offspring were fixed with formaldehyde, and the inferior vermis
of each cerebella was removed and processed for histologic observations.
Purkinje cell density in the uvula was determined in sagittal serial
sections. There was no significant difference between control and
experimental animals in the number of Purkinje cells per mm of Purkinje
cell line (linear density), as well as in the density of Purkinje cells
in the Purkinje cell layer.

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Study Type: Nervous System, Cellular and Subcellular Effects;
IN VIVO; SQUIRREL MONKEY
Effect Type: Effects of in-utero and postnatal chronic exposure to RFR
on brain development as determined by counting Purkinje cells in
sections of the cerebellar uvula.
Frequency: 2.45 GHz
Modulation: Amplitude modulated
Power Density: 10 mW/sq cm Av
SAR: 3.4 W/kg

EXPOSURE CONDITIONS: Pregnant squirrel monkeys were exposed to 2.45-GHz
RFR for 3 hr/day, 5 days/week, starting on gestational day 35, in a set
of multimode, mode-stirred cavity/cage modules, each partitioned to
expose 2 monkeys concurrently, as described in Kaplan et al. (1982).
After parturition, each dam and its infant was exposed as a dyad (with 2
dyads per module) for 9.5 additional months. A magnetron fed from a
phase-controlled half-wave-doubler power supply was used as the source
for each cavity. Thus, the RFR output was modulated by a combination 60
Hz, the rotation of the mode stirrer, and the movement of the animals
within each module. Other pregnant squirrel monkeys and their offspring
were concurrently sham-exposed in similar modules (with the RFR off).
All the modules were within a room maintained at constant temperature
and humidity.

OTHER INFORMATION: Because of the unavailability of a twin-well
calorimeter suitable for squirrel monkeys at the time the study by
Kaplan et al. (1982) was done, the dosimetry was performed on 2
identical rubber dolls, approximately the size of an adult squirrel
monkey, filled with 1 kg of saline and enclosed individually in 5-cm-

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postnatal exposure to RFR could temporarily affect the migration pattern of the Purkinje cells but not the proliferative activity of the external granular layer.

Although the positive results above appear to be statistically valid (from use of the t-test), they are questionable because the normalized SDs (ratio of SD to its mean value) for the RFR groups were virtually the same as for their respective sham-exposed groups. In view of the large variations in mean SAR at 2.45 GHz stated by the authors (0.5 to 6 W/kg), one would expect to observe some dose dependence of effect among the RFR-exposed animals that would be manifested as much larger values of normalized SDs than for the sham-exposed animals.

It is also difficult to assess the biological significance of the positive findings in the absence of similar studies by other investigators, especially since Albert et al. (1981b) obtained nonsignificant effects on counts of Purkinje cells from the cerebellar uvulae of squirrel monkeys chronically exposed to 2.45-GHz RFR at 10 mW/sq cm (3.4 W/kg) prenatally and postnatally. Moreover, in the present paper and a previous one (Albert and DeSantis, 1975), the authors reported the absence of RFR-induced degenerative or other morphologic changes in Purkinje cells.

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EFFECT OF NONIONIZING RADIATION ON THE PURKINJE CELLS OF THE UVULA IN
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Bioelectromagnetics, Vol. 2, No. 3, pp. 241-246 (1981b)

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Smialowicz, R.J., J.S. Ali, E. Berman, S.J. Bursian, J.B. Kinn, C.G.
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CHRONIC EXPOSURE OF RATS TO 100-MHZ (CW) RADIOFREQUENCY RADIATION:
ASSESSMENT OF BIOLOGICAL EFFECTS
Radiat. Res., Vol. 86, pp. 488-505 (1981b)

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All cell counts were performed double blind by two individuals. The results were presented in terms of the mean density of Purkinje cells (number per sq mm) and standard error (SE) for the RFR- and sham-exposed groups.

In experiment 1, the pregnant rats delivered their pups within 12 hr after completion of their RFR- and sham-exposures and return to GWU. Three of the 6 pups exposed prenatally to RFR and 3 of the 6 pups sham-exposed prenatally were euthanized on postnatal day 1, and the remaining 3 pups of each group were euthanized 40 days after birth. The cerebella from the day-1 pups were not mature enough for clear discernment of the Purkinje cells, so no data were presented. The results for the RFR-exposed 40-day pups were 35.87 +/- 1.71 cells/sq mm, as compared with 48.47 +/- 2.26 cells/sq mm for the sham-exposed 40-day pups. The 25.8% decrease for the RFR pups was significant ($p < 0.01$).

In experiment 2, 3 pups exposed to RFR and 3 pups that were sham-exposed postpartum were euthanized immediately after their return to GWU and the other 3 of each were euthanized 40 days after cessation of RFR- or sham exposure. For the pups euthanized immediately, the results were 87.46 +/- 4.62 cells/sq mm for the RFR-exposed pups and 115.68 +/- 5.30 cells/sq mm for the sham-exposed pups. The difference was significant ($p < 0.01$). For the 40-day pups, the values were 31.61 +/- 1.22 and 33.98 +/- 1.05 cells/sq mm, respectively, a nonsignificant difference ($p < 0.1$).

In experiment 3, the pups that were sham-exposed or exposed to 100-MHz RFR both in utero and postpartum were delivered to GWU 14 months after completion of the exposure regimen and were euthanized immediately. The results were 24.74 +/- 0.71 and 28.33 +/- 1.21 for the RFR-exposed and sham-exposed pups, respectively. The difference was significant ($p < 0.05$).

CRITIQUE: The authors noted that the cerebellar rudiment and the Purkinje cells arise during the second half of gestation. They suggested that the significantly smaller Purkinje-cell counts obtained in experiments 1 and 3 (both of which involved exposure to RFR during that half of the prenatal period) could be due to reduction of the proliferative activity of the neuroepithelium by the RFR, or that the RFR could affect the migratory pattern of Purkinje cells and other microneurons in a manner that prevents the Purkinje cells from reaching the molecular-granular interface. (The authors stated that these points will be discussed in a separate manuscript.) The observation of smaller cell counts both at 40 days and 14 months after completion of RFR exposure was taken as indicating the permanence of this effect of prenatal exposure.

The results of experiment 2, in which significantly smaller Purkinje-cell counts were obtained for the pups exposed postnatally to RFR and euthanized immediately and the nonsignificant difference in counts between the groups euthanized 40 days after RFR-and sham exposure, were taken as an indication of the reversibility of this effect. Presumably because brain cells are not regenerative, the authors suggested that

sessions for feeding. During all periods of no exposure (including intersessions), the pups were reunited with their dams in conventional cages.

In experiments 1 and 2, the rats were transported from George Washington University (GWU) to the Bureau of Radiological Health (BRH) for the exposure regimen and were returned to GWU for study after completion thereof.

In experiment 3, 4 pregnant rats were exposed concurrently to 100-MHz CW RFR at 46 mW/sq cm (SAR 2.77 W/kg) in a transverse electromagnetic (TEM) cell (described in Smialowicz et al., 1981b) at the Environmental Protection Agency, North Carolina (EPA). Exposures were performed during 8:00 am-2:00 pm daily on gestation day 6 through term, after which the offspring were exposed 4 hr daily for 97 days. Four other pregnant rats and their pups were similarly treated but sham-exposed. The treated offspring were delivered to GWU 14 months after cessation of exposure.

OTHER INFORMATION: For experiments 1 and 2 (2.45 GHz), a nonperturbing probe was used to measure power densities within each empty Plexiglas cage with and without subjects in the other cages. The results indicated that the values varied with location within the cage and with time, due to rat movements in the other cages (no data presented). Thus, it was determined that at an average power density of 10 mW/sq cm, the power density might vary with time from 4 to 30 mW/sq cm. From Durney et al. (1978), the corresponding time-averaged SAR for each pregnant rat was about 2 W/kg with a range from 0.5 to 6 W/kg. For experiment 3 (100 MHz), the mean SARs at 46 mW/sq cm ranged from 2 W/kg for pregnant rats to 3 W/kg for neonates, with intermediate values for older pups (from Smialowicz et al., 1981b).

The development of the mammalian brain is dependent on migration of nerve cells, the patterns of which are well understood for the cerebellum. The cerebellar Purkinje cells were selected for study because they provide a relay station for major input to, and output from, the cerebellum and are readily identifiable in the interface between the molecular and granular layers.

In all three experiments, the brain of each RFR-exposed animal was processed with its corresponding sham-exposed control. After anesthesia, each rat was fixed with formalin by cardiac perfusion and the cerebella were removed, divided in the midsagittal plane, embedded in paraffin, serially sectioned (10 micrometers thick), and stained. Six to nine parasagittal planes were selected and used as constant reference levels for matching cerebellar sections from RFR- and control rats. Four to six serial sections were studied at each plane. Each section was projected, the boundaries of various regions were outlined, the areas within the boundaries of interest were determined with a planimeter, and the Purkinje cells within the molecular-granular interface were counted. (Cells without visible nucleoli were not counted.)

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Albert, E.N., M.F. Sherif, N.J. Papadopoulos, F.J. Slaby, and J.
Monahan
EFFECTS OF NONIONIZING RADIATION ON THE PURKINJE CELLS OF THE RAT
CEREBELLUM

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AUTHOR ABSTRACT: In one experiment, Sprague Dawley rats (16-21 days of
gestation) and their offspring were exposed to 100-MHz (CW)
electromagnetic radiation at 46 mW/sq cm (SAR 2.77 mW/g) for 4 h/day for
97 days. In another experiment, the pregnant rats were irradiated daily
from 17 to 21 days of gestation with 2450-MHz (CW) microwaves at 10
mW/sq cm (SAR 2 mW/g) for 21 h/day. In a third experiment, 6-day-old
rat pups were irradiated 7 h/day for five days with 2450-MHz radiation
at 10 mW/sq cm. Equal numbers of animals were sham irradiated in each
group.

Quantitative studies of Purkinje cells showed a significant and
irreversible decrease in rats irradiated during fetal or fetal and early
postnatal life. In animals exposed postnatally, and euthanized
immediately after irradiation, significant decrease in the relative
number of Purkinje cells was apparent. However, restoration apparently
occurred after 40 days of recovery.

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Study Type: Nervous System, Cellular and Subcellular Effects;
IN VIVO; RAT
Effect Type: Effects of prenatal, postnatal, and perinatal exposure of
rats to RFR on brain development as determined by counting Purkinje
cells in sections of the cerebellum
Frequency: 100 or 2450 MHz
Modulation: CW
Power Density: 46 mW/sq cm at 100 MHz, 10 mW/sq cm at 2450 MHz
SAR: 2-3 W/kg at 100 MHz, 2 W/kg at 2450 MHz

EXPOSURE CONDITIONS: In experiment 1, 6 pregnant rats, each housed in a
ventilated Plexiglas container, were exposed concurrently in groups of 3
from above with a truncated horn to 2.45-GHz CW RFR at 10 mW/sq cm in
one of two anechoic chambers. Exposures were for 21 hr/day for 5 days,
starting on gestation day 17. During the exposure regimen, the rats
were moved for 1.5 hr twice daily to conventional rat cages, where food
and water were available ad libitum. Six other rats were similarly
treated but sham-exposed in the other anechoic chamber.

In experiment 2, 6 matched pairs of 6-day-old litter mates were used.
One of each pair in a ventilated Plexiglas cage was exposed to 2.45-GHz
CW RFR 7 hr/day for 5 days in one of the anechoic chambers while the
other was sham-exposed in the other chamber. Daily exposure sessions
were for 3.5 hr each in the morning and afternoon, with 1.5 hr between

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Pappas, B.A., H. Anisman, R. Ings, and D.A. Hill

ACUTE EXPOSURE TO PULSED MICROWAVES AFFECTS NEITHER PENTYLENETETRAZOL
SEIZURES IN THE RAT NOR CHLORDIAZEPOXIDE PROTECTION AGAINST SUCH
SEIZURES

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AUTHOR ABSTRACT: Three experiments failed to provide consistent
evidence for an effect of 2.70 GHz pulsed microwave radiation up to 20
mW/sq cm on pentylenetetrazol-induced seizures or on the efficacy of
chlordiazepoxide for counteracting such seizures. Microwave radiation
counteracted the hypothermic effects of chlordiazepoxide without
altering its antiseizure efficacy. This underscores the dissociation
between thermal and pharmacological effects of microwaves.

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Study Type: Nervous System, Multiagent Interactions, Physiology and
Biochemistry; IN VIVO; RAT
Effect Type: RFR-induced alterations of the effects of seizure- and
antiseizure drugs
Frequency: 2.7 GHz
Modulation: 2-microsecond pulses at 500 pps (0.001 duty cycle)
Power Density: 5, 10, 15, or 20 mW/sq cm Av
SAR: 0.75, 1.5, 2.25, or 3.0 W/kg

EXPOSURE CONDITIONS: In experiment 1, rats in individual circular
acrylic cages spaced about 3 wavelengths apart in an anechoic chamber
were exposed from above in pairs for 30 min to far-field, circularly
polarized RFR at 0 (sham), 5, 10, or 15 mW/sq cm. Prior to exposure,
each rat was weighed, its rectal temperature was recorded, and it was
injected i.p. with 1.0 ml/kg of saline. After exposure, the rectal
temperatures of the rats were recorded again; the rats were injected
i.p. with the seizure-inducing drug pentylenetetrazol (PTZ) at 0, 20,
40, 60, 70, or 80 mg/kg in 1.0 ml/kg of saline; and seizure activity was
studied.

In experiment 2, the rectal temperature of each rat was measured and the
rat was injected with chlordiazepoxide (CDZ) at 2.0, 7.5, or 15.0 mg/kg
prior to exposure. Exposures were for 30 min at 0, 5, 10, or 15 mW/sq
cm in factorial combination with the CDZ doses. After exposure, the
rectal temperatures were measured again, the rats were injected i.p.
with 70 mg/kg of PTZ, and the strength of CDZ inhibition of seizure
induction by PTZ was studied.

Part 1 of experiment 3 was done to check some results of experiment 1;
rats were injected with 60 mg/kg of PTZ after exposure at 0, 5, 10, 15,
or 20 mW/sq cm. In part 2 of experiment 3, designed to check some
results of experiment 2, rats were injected with 7.5 mg/kg of CDZ prior
to, and with 70 mg/kg of PTZ after, exposure at those power densities.

The effect of each treatment on seizure activity was determined.

OTHER INFORMATION: SARs were determined by measuring rectal-temperature increases for rats anesthetized with sodium pentobarbital (45 mg/kg) and singly exposed for 3 min at 144 mW/sq cm. With corrections for heat loss in rats sham-exposed for 3 min, the results yielded 1.5 +/- 0.1 W/kg for 10 mW/sq cm.

For 8 min after injection of PTZ, the rats were watched for signs of seizure activity. The latency interval to the onset of the first sign was recorded and the seizure intensity was rated in accordance with the following scale:

    0) No seizure, normal exploratory activity
    1) 0 followed by loss of muscle tone and reduced spontaneous
       activity
    2) 0 followed by jerking forelimb extensions and lateral support by
       the hindlimbs
    3) 0 and 2 followed by torsion of the anterior body; quadruped
       stance may be lost momentarily
    4) 0, 2, and 3 followed by a bout of wild running and tonic-clonic
       convulsions with a 99% mortality

The average preexposure core temperature for all the rats was 36.8 +/- 0.2 (SEM) deg C. In the first experiment, the postexposure mean core-temperature increases were 0.5, 0.74, 0.75, and 1.35 deg C for 0, 5, 10, and 15 mW/sq cm, respectively. By analysis of variance with body weight as the covariate and temperature increase as the dependent variable, body weight accounted for a significant amount of the variability, and RFR exposure was the main effect; although sham-exposure yielded a rise of 0.5 deg C, the RFR-induced increases were significantly ($p < 0.05$) larger.

In the first experiment, latency-to-seizure times after PTZ injection decreased with increased PTZ dose for all power densities, with an asymptote (about 50 seconds) reached at 60 mg/kg. Analysis of variance with PTZ dose and RFR power density as independent variables showed a significant ($p < 0.001$) effect of dose: Post-hoc analysis with Tukey's test indicated that although the 60-, 70-, and 80-mg/kg groups did not differ from one another (asymptote region), all other between-group comparisons were significant. The analysis of variance also showed a slight but significant ($p < 0.032$) main effect of RFR. As seen in post-hoc analysis, the rats exposed at 15 mW/sq cm exhibited significantly ($p < 0.05$) shorter latencies than the sham-exposed rats; averaged across PTZ doses, the mean latencies were 82.9 and 89.4 seconds, respectively. However, the analysis of variance showed no interaction between PTZ dose and RFR power density.

The mean seizure-intensity score vs PTZ dose in the first experiment ranged monotonically from 0 at 0 mg/kg to about 3.8 at 80 mg/kg, with no apparent effect of power density. Analysis of variance with PTZ dose and RFR power density as independent variables showed a significant

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(p<0.001) effect of dose, with each dose yielding a significantly
(p<0.05) higher seizure intensity than all lower doses. The analysis
also revealed a significant (p<0.02) main effect of power density.
Post-hoc analysis (Tukey's test) indicated that the mean seizure
intensity was greater for rats exposed at 15 mW/sq cm than at 5 mW/sq cm
(p<0.05), but that none of the values for the RFR groups differed
significantly from that for the sham-exposed group. Again there was no
interaction between PTZ dose and RFR power density.

The authors suggested that the significant changes in seizure latency
and intensity at 15 mW/sq cm obtained in the first experiment could have
been due to local brain hyperthermia rather than to alteration of the
effect of PTZ on brain neuronal activity.

For the second experiment, the doses of CDZ used to inhibit PTZ-induced
seizures were derived from unpublished results of a pilot study by
Pappas, Anisman, and Ings. They had found that 2.0, 7.5, and 15 mg/kg
of CDZ respectively caused minimal, modest, and maximal attenuation of
the seizure-inducing effects of 70 mg/kg of PTZ.

Analysis of variance of the core-temperature changes in the second
experiment showed significant main effects for both CDZ dose (p<0.001)
and power density (p<0.001), with no interaction between them. Core
temperature was progressively reduced from baseline (37.7 deg C) with
increasing CDZ dose. After collapsing the data over power density, the
temperature reductions at 7.5 and 15.0 (but not at 2.0) mg/kg were
significant relative to the mean core temperature of the saline-control
group, and the reduction at 15.0 mg/kg was significantly larger than at
7.5 mg/kg, which, in turn, was significantly larger than at 2.0 mg/kg
(p<0.01, Tukey's test). Collapsing the data over CDZ dose indicated
that only 15 mW/sq cm significantly increased the core temperature
relative to that of the sham-exposed group (p<0.01).

Analysis of variance of the seizure-onset latencies in the second
experiment indicated that CDZ significantly (p<0.001) increased the
latency time in a clearly dose-dependent manner. The analysis also
showed a main effect of power density (p<0.001) and a significant
(p<0.001) CDZ-RFR interaction. However, the effect of the RFR was shown
by subsequent analysis to be ascribable to two observations: that rats
given 7.5 mg/kg of CDZ showed longer latencies after exposure at 15
mW/sq cm than after 0, 5, or 10 mW/sq cm; and that rats given 15 mg/kg
had shorter latencies after exposure at 5 mW/sq cm than at 0, 10, or 15
mW/sq cm (p<0.01, Tukey's test).

Analysis of variance of the seizure-intensity scores of the second
experiment indicated significant main effects of CDZ dose (p<0.001) and
power density (p<0.01), and a significant interaction between them
(p<0.01). All CDZ doses except 2.0 mg/kg significantly (p<0.01) lowered
seizure intensity relative to saline controls at every power density.
However, the RFR effect was entirely accounted for by only one
difference: The group given 7.5 mg/kg of CDZ and exposed at 15 mW/sq cm
showed a significantly lower seizure intensity than its corresponding

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sham-exposed group.

Thus, the only consistent effect of RFR on the two seizure parameters in the second experiment was for rats given 7.5 mg/kg of CDZ; exposure at 15 mW/sq cm increased their latency-to-seizure times and reduced the intensity of their seizures. The authors noted that 7.5 mg/kg was close to the threshold dose for protection against seizure and they reasoned that RFR exposure may be effective only near the dose threshold, i.e., 15 mg/kg of CDZ already provided effective protection and that 2.0 mg/kg offered virtually none. Another possibility suggested by them was that the apparent positive findings were ascribable to random (Type II) statistical error. The third experiment was performed to test these hypotheses.

In the third experiment, groups of rats were exposed at 0, 5, 10, 15, or 20 mW/sq cm for 30 min, after which they were given 60 mg/kg of PTZ; other groups of rats were given 7.5 mg/kg of CDZ, exposed at those levels of RFR, and subsequently given 70 mg/kg of PTZ. Temperatures and seizure data were obtained as before. The principal experimenter was unaware of the level of RFR administered to each rat. (Presumably this was not the case in the previous experiments.)

Analysis of variance of the core-temperature data for the rats injected only with PTZ showed a significant (p<0.001) effect of power density; by Tukey's test, temperature elevations relative to sham-exposed rats were significant for 10 mW/sq cm or higher. However, there was no significant relationship between power density and latency-to-seizure time or seizure-severity score. For the rats injected with CDZ before RFR exposure, analysis of variance of the temperature data again showed a significant (p<0.001) effect of power density, but by Tukey's test, only the mean temperature of the rats exposed at 20 mW/sq cm differed significantly (p<0.01) from that of the sham-exposed rats.

Comparison of the temperature-vs-power-density curves of the CDZ/PTZ rats and PTZ-only rats indicated that the hyperthermic effects of RFR exposure were attenuated by CDZ and/or that the hypothermic effects of CDZ were counteracted by RFR exposure. However, analysis of variance of the seizure data for the CDZ/PTZ rats showed no significant effect of power density on either latency or severity. Thus, despite the thermal antagonism between RFR and CDZ, the RFR did not alter the protective efficacy of this CDZ dose against PTZ-induced seizure.

In their discussion of the third experiment, the authors stated: "This experiment, which employed a more rigorous (rater blind) seizure scoring procedure than our earlier experiments, failed to support the hints from those experiments that high (15 mW/sq cm) or even higher (20 mW/sq cm) pulsed microwave power densities enhance PTZ seizures and increase the antiseizure protection afforded by 7.5 mg/kg of CDZ. We conclude that these earlier hints which were restricted to only a few of the many possible comparisons represented spurious, Type II statistical errors although we cannot, of course, rule out the possibility of experimenter bias." They also noted the following, with appropriate citations: "It

is currently believed that PTZ induces seizures by blocking the inhibitory effects of the neurotransmitter GABA as well as by a direct effect on neuronal membranes. Conversely, chlordiazepoxide, which as shown here effectively blocks PTZ seizures, appears to facilitate GABA transmission through a postsynaptic action. From the present experiments in which microwaves reliably affected neither PTZ nor CDZ action, it would appear that brief, acute exposure to such radiation has no pharmacologically significant effect upon GABA neurons."

CRITIQUE: The experimental design of this study, the statistical treatment of the data, and the lucid presentation of the results are commendable. (There is one totally inconsequential error in the PTZ-dose abscissas of Fig. 1: the spacing of the 70 marker from the 60 and 80 markers should be half that shown.) In particular, the inclusion of saline-injected controls and sham-exposed groups as well as adequate numbers of rats in all groups lends much confidence in the findings.

As noted by the authors, their negative results appear to be at variance with those of Thomas et al. (1979). Thomas et al. (1979) trained rats to respond on a food-reward, fixed-interval (FI) behavior schedule and found that exposure to 2-microsecond pulses of 2.45-GHz RFR at 500 pps (average power density of 1 mW/sq cm) did not alter their behavior. These investigators also established a dose-effect relationship for CDZ over the range from 1 to 40 mg/kg on the FI behavior schedule. They then found that exposure to the RFR immediately after administering CDZ yielded a dose-effect curve of the same shape as that without the RFR but of about twice the magnitude. Reasons for the differences in the findings of the two investigations (other than the widely differing biological endpoints) would be speculative.

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Science, Vol. 203, pp. 1357-1358 (1979)

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Adair, E.R., B.W. Adams, and G.M. Akel
MINIMAL CHANGES IN HYPOTHALAMIC TEMPERATURE ACCOMPANY MICROWAVE-INDUCED
ALTERATION OF THERMOREGULATORY BEHAVIOR

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AUTHOR ABSTRACT: This study probed the mechanisms underlying microwave-
induced alterations of thermoregulatory behavior. Adult male squirrel
monkeys (Saimiri sciureus), trained to regulate the temperature of their
immediate environment (Ta) behaviorally, were chronically implanted with
Teflon reentrant tubes in the medial preoptic/anterior hypothalamic area
(PO/AH), the brainstem region considered to control normal
thermoregulatory processes. A Vitek temperature probe inserted into the
tube measured PO/AH temperature continuously while changes in
thermoregulatory behavior were induced by either brief (10-min) or
prolonged (2.5-h) unilateral exposures to planewave 2,450-MHz continuous
wave (CW) microwaves (E polarization). Power densities explored ranged
from 4 to 20 mW/sq cm (rate of energy absorption [SAR] = 0.05 W/kg per
mW/sq cm). Rectal temperature and four representative skin temperatures
were also monitored, as was the Ta selected by the animal.

When the power density was high enough to induce a monkey to select a
cooler Ta (8 mW/sq cm and above), PO/AH temperature rose about 0.3 deg C
but seldom more. Lower power densities usually produced smaller
increases in PO/AH temperature and no reliable change in
thermoregulatory behavior. Rectal temperature remained constant while
PO/AH temperature rose only 0.2-0.3 deg C during 2.5-h exposures at 20
mW/sq cm because the Ta selected was 2-3 deg C cooler than normally
preferred. Sometimes PO/AH temperature increments greater than 0.3 deg
C were recorded, but they always accompanied inadequate thermoregulatory
behavior. Thus, a PO/AH temperature rise of 0.2-0.3 deg C, accompanying
microwave exposure, appears to be necessary and sufficient to alter
thermoregulatory behavior, which ensures in turn that no greater
temperature excursions occur in this hypothalamic thermoregulatory
center.

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Study Type: Metabolism and Thermoregulation, Behavior, Nervous System,
Physiology and Biochemistry; IN VIVO; SQUIRREL MONKEY
Effect Type: Behavioral thermoregulation in response to RFR-induced
hypothalamic temperature increases
Frequency: 2.45 GHz
Modulation: CW
Power Density: 4-20 mW/sq cm
SAR: 0.6-3.0 W/kg

EXPOSURE CONDITIONS: Each monkey was exposed to vertically-polarized
far-field RFR propagated horizontally from a standard-gain horn within
an anechoic chamber. For exposure, the monkey was seated in a Plexiglas

restraining chair, with its right side toward the horn, within a Styrofoam box through which the flow of air at either 10 or 50 deg C could be controlled (within a prescribed paradigm) by the monkey with a valve.

Short-duration exposures were for 10 min each at 4, 6, 8, 10, 12, and 14 mW/sq cm in succession, with 10 min between exposures (threshold series) or for 10-min periods at 10 mW/sq cm, with 10 min between exposures (repetitive series). Long-duration exposures were single 2.5-hr continuous sessions at 20 mW/sq cm. Exposures were conducted after appropriate behavioral-thermoregulation-stabilization periods. Auditory cuing was minimized by 73 dB of masking noise.

OTHER INFORMATION: In a pilot study, nonperturbing Vitek temperature probes were implanted in the medial preoptic nucleus of the anterior hypothalamus (PO/AH) of two squirrel monkeys and in the midbrain reticular formation (MB) of one of the monkeys. Each animal, under anesthesia, was placed in the exposure chamber and equilibrated to a circulating air temperature (Ta) of 35-36 deg C so that rectal temperature would remain constant at about 38 deg C. The monkey was then exposed to 2.45-GHz CW RFR for 10 min at each of several power densities while brain temperatures were recorded continuously.

The results (displayed in Fig. 1 of the paper) were temperature rises in the PO/AH and the MB ranging from about 0.2 deg C at 6 mW/sq cm to about 0.8 deg C at 20 mW/sq cm, with small differences between the monkeys or the two brain regions. Also indicated was that exposure at 6-8 mW/sq cm yielded a PO/AH temperature increase of 0.2-0.3 deg C, previously found to be the threshold temperature necessary to initiate thermoregulation (induced with an implanted thermode) in conscious squirrel monkeys (Adair et al., 1970). The purpose of the present study was to extend those results with RFR-exposed anesthetized animals to RFR-induced behavioral thermoregulation by conscious squirrel monkeys.

The three adult male squirrel monkeys used in the present study were highly trained to regulate environmental temperature behaviorly and had previously participated in various behavioral experiments, many of which involved multiple exposures to RFR in the range from 2 to 20 mW/sq cm. Two of the monkeys had been chronically exposed to 2.45-GHz CW RFR for 15 weeks at 1 mW/sq cm one year prior to the present study; no changes in normal thermoregulatory processes had been detected with behavioral and physiological tests conducted during and after exposure.

Prior to the current experiments, a pair of sealed Teflon reentrant tubes of size suitable for insertion of Vitek temperature probes were surgically implanted in the PO/AH, and the animals were allowed to recover for at least 10 days before conducting the experiments. In the experimental arrangement, cool air (10 deg C) was circulated at 0.36 m/s through the Styrofoam box containing the monkey. Available to the monkey was a cord that actuated a lever to obtain warm air (50 deg C) when pulled. The warm air automatically flowed for 15 seconds, after which the flow of cool air was resumed. (Presumably, additional pulls

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during any such 15-second period were without consequence.) After several hours of training, the monkeys routinely responded at a rate that yielded a time-averaged air temperature (mean Ta) of 35-36 deg C.

SARs were assessed from calorimetric measurements in saline-filled cylindrical phantoms, as described in Adair and Adams (1980a). The measurements yielded 0.15 W/kg per mW/sq cm. (The value 0.05 in the abstract appears to be a typographical error.) During exposure, PO/AH temperature and Ta were recorded continuously. In addition, rectal temperature (Tre) and temperatures at four skin locations (tail, leg, abdomen, and foot) were read once a minute with thermocouples arranged to minimize field effects. A mean skin temperature (Tsk) was calculated by appropriately weighting the four skin measurements.

Baseline behavioral-thermoregulation data were obtained for each monkey in 5 presurgical non-RFR sessions, each of 4-hr duration, during which the animal selected its preferred values of Ta while Tre and Tsk were monitored continuously. In one postsurgical session, changes in body temperatures were measured for each conscious monkey during 10-min exposures at 4, 6, 8, 10, and 20 mW/sq cm without behavioral control of Ta, i.e., with Ta held constant at 34 deg C (thermoneutrality). Also, the metabolic heat production of each monkey was determined from its oxygen consumption, as described in Adair and Adams (1982). Preceding the series of exposures was a 90-min period of equilibration to the constant Ta, and interexposure intervals of 10-15 min were sufficient to restabilize the monkey after each exposure.

The results were presented in Fig. 3. All body temperatures increased monotonically with power density. Foot-skin temperature, plotted separately from weighted-mean skin temperature, showed a discontinuity between 8 and 10 mW/sq cm (sharper rise than at lower power densities), which was ascribed to vasodilation of the peripheral blood vessels of the foot. The values of rectal and PO/AH temperature at corresponding power densities differed little from each other except perhaps at 20 mW/sq cm, where the latter was larger than the former. However, the number of animals was too small for ascribing statistical validity to the difference. At 6 and 8 mW/sq cm, respectively, mean increases of 0.15 and 0.25 deg C in PO/AH temperature occurred, essentially the same as those obtained with the anesthetized monkeys. At 10 and 20 mW/sq cm, the increases in PO/AH temperature in the anesthetized animals were larger than in conscious monkeys with intact thermoregulation. From Fig. 3, metabolic heat production decreased by 1 W/kg at 4 mW/sq cm, was essentially unchanged at 6-10 mW/sq cm, and increased by 1 W/kg at 20 mW/sq cm. The authors noted that these changes in metabolic heat production were within the normal range of variability of this thermoregulatory response at a Ta of 34 deg C.

In the "threshold" series of experiments, Ta was subject to behavioral thermoregulation by each monkey. After a 2-hr period of behavioral stabilization, two of the monkeys were exposed successively at 4, 6, 8, 10, and 12 mW/sq cm for 10 min each, with interexposure intervals of 10 min. The third monkey was similarly treated, but a 10-min exposure at

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14 mW/sq cm was added to the set. Five sets were conducted on each monkey.

For two of the monkeys, the mean Ta values (and SEMs) selected during the successive 10-min intervals (including those during the 2-hr preexposure stabilization period) were plotted vs time in Fig. 4. For comparison, superposed on the plot for each animal were its presurgical baseline Ta values vs time. The RFR threshold for alteration of thermoregulatory behavior was defined by the authors as the lowest power density that yielded a statistically-significant ($p < 0.05$, t-test) lower value of mean Ta than the baseline mean Ta for the corresponding 10-min interval, subject to the additional requirement that the difference at the next higher power density also be significant. The threshold values for these two monkeys were 8 and 12 mW/sq cm. The value for the third monkey (data not displayed) was stated to be 10 mW/sq cm.

Also plotted in Fig. 4 for the two monkeys were their mean PO/AH-, rectal-, and skin temperatures vs time. Associated with the threshold power density for each animal was a rise of 0.2-0.3 deg C in the PO/AH temperature but no discernible change in Tre. The rises in mean PO/AH temperature at power densities above the threshold were 0.3 deg C except for the monkey whose final exposure was at 14 mW/sq cm, for which the rise was 0.4 deg C.

The authors also stated the following: "Another notable result concerns the rise in preoptic temperature associated with the power density just BELOW the threshold level (always antecedent to the threshold power density in the ascending series). For two of the three monkeys tested, this temperature rise was 0.3 deg C."

The protocol for the "repetitive" series of experiments was the same as for the threshold series, but the successive 10-min exposures were at 10 mW/sq cm instead of an ascending set and there were 4 instead of 5 sessions with each monkey. The combined results for two monkeys (8 sessions) were plotted in Fig. 5 in the same format as before. These showed that the mean Ta selected during the first 10-min exposure was within the preexposure range and was at least 1 deg C warmer than those selected during the subsequent exposures. The minimal behavioral change during the initial exposure was accompanied by mean rises of 0.4 deg C in Tsk, 0.5 deg C in Tre, and 0.5 deg C in PO/AH temperature. These rises were significantly larger than those for the later exposures and were ameliorated somewhat during the later exposures by monkey selection of substantially lower values of Ta, a result confirming a previous finding (Adair and Adams, 1983). From Fig. 5, the lowest value of mean Ta (about 33.7 deg C) was selected during the third 10-min exposure, a possible indication of adaptation to the RFR.

In the final series of experiments, each study session of behavioral thermoregulation consisted of 90 min of preexposure stabilization, 2.5 hr of continuous exposure at 20 mW/sq cm, and 10 min of postexposure. Each of the three monkeys participated in 5 sessions and the data for each were analyzed separately. The results for two monkeys were

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presented in Figs. 6 and 7 in the same format as before (i.e., mean values of ambient-, PO/AH-, rectal-, and weighted-skin temperature at 10-min intervals). The SEM for each mean Ta was displayed. Also plotted were the baseline (presurgical) values of mean Ta (and SEM) at corresponding 10-min epochs. The authors indicated that the SEMs for the values of Tre, Tsk, and PO/AH temperature were too small to display.

The stabilization process for one of the monkeys during the 90-min preexposure period was clearly evident in Fig. 6; at the first 10-min epoch, the Ta was 36.0 deg C; it then dropped to a minimum of 32.5 deg C at 30 min and rose sharply at 40 min to a plateau of about 34 deg C for the remaining 50 min. The mean Ta selected by that subject during RFR exposure dropped to a minimum of 29.5 deg C at 120 min (30 min of exposure), rose nonmonotonically to about 32 deg C at 240 min (exposure end), and rose sharply to 34.5 deg C during the 10-min postexposure interval. The results for the other monkey (Fig. 7) were similar: a minimum Ta of 31.5 deg C at 110 min (20 min of exposure), a nonmonotonic rise to 33.3 deg C at exposure end, and a sharp postexposure rise to 36 deg C.

For both animals, the PO/AH temperature rose 0.4-0.5 deg C during the first 10 min of exposure while the skin and rectal temperatures changed relatively little, and the monkeys quickly reduced the Ta by 2-3 deg C as noted above. This thermoregulatory behavior prevented further rises in PO/AH temperature while ensuring the stability of skin and rectal temperatures. During the 10-min postexposure interval, the PO/AH temperature returned to its preexposure level in each case.

In their discussion, the authors noted that the finding of a threshold power density for induction of reliable behavioral thermoregulation confirmed their previous results (Adair and Adams, 1980a, 1983) and those of Stern et al. (1979). The data showed that the hypothalamus was directly involved in the generation of the threshold response, and that the temperature rise in the hypothalamus at the threshold was about 0.3 deg C and was seldom exceeded at superthreshold power densities. The authors also noted, however, that the requisite RFR-induced rise in PO/AH temperature did not always induce behavioral thermoregulation, and therefore that thermosensitive tissues other than the hypothalamus, such as cutaneous thermodetectors, may also contribute to thermoregulatory behavior. They then presented preliminary results of an experiment in which perfusion of the other tube implanted in the PO/AH with a heated nonaqueous fluid was used to manipulate the PO/AH temperature in the absence or presence of RFR. In the experiment, after the usual 90-min equilibration period, a monkey was given four 20-min treatments with 20-min intervals between them. Exposure at 20 mW/sq cm were the first and third treatments. The second treatment was heating the PO/AH with the fluid while the animal was exposed to the RFR and the fourth treatment was heating the PO/AH with the fluid only.

The results, presented in Fig. 8 in the same format as before, showed Ta reductions during treatments 1 and 3 similar to those obtained before. Concurrently, PO/AH-, rectal-, and skin temperatures rose approximately

linearly during each treatment. Also noteworthy was a sharp rise in foot-skin temperature, particularly during treatment 1, an indication of the occurrence of peripheral vasodilation. The authors surmised that this process could stimulate the cutaneous thermodetectors and thereby provide a peripheral cue for altering thermoregulatory behavior.

By contrast, the dips in Ta were much deeper during treatments 2 and 4, to a minimum of about 23 deg C for treatment 2 (concurrent RFR and fluid) and 27 deg C for treatment 4 (fluid only). Moreover, the PO/'H temperature rose sharply to a peak well in excess of 0.3 deg C within the first few minutes of each treatment and then declined approximately linearly during the remainder of the period to a value below that at the start of the treatment. These changes were accompanied by linear decreases in rectal- and skin temperature. The authors concluded that localized PO/AH heating (by thermode, for example) stimulates vigorous heat-loss responses, whereas whole-body heating by RFR can result in heat storage.

CRITIQUE: The reasons for not presenting similar data for all three monkeys tested in this study were not stated.

Although the power-density-threshold criteria defined by the authors were logical, the cited threshold value for at least one of the monkeys (S:Dumbo, 12 mW/sq cm) seems open to question because of the variations with time of the mean baseline values of Ta used for comparison. These variations were comparable to the behavioral changes of Ta induced by RFR exposure, so there was little justification for comparing baseline and RFR-related Ta values at corresponding epochs. The baseline data for the monkey with the 8-mW/sq-cm threshold (S:Whitehead) were far less variable, thus providing greater credence to this result. The threshold for the third monkey was stated to be 10 mW/sq cm, but the data were not presented.

The quotation in the previous section regarding the rise in preoptic temperature at just below the threshold power density was not evident in Fig. 4 for either subject; instead, rises in PO/AH temperature (less than 0.3 deg C) were readily discernible at all of the subthreshold power densities. However, there was a distinct increase in mean skin temperature of both monkeys at the power density just below each threshold.

Despite the minor points above, the preponderance of the results of this and other related studies clearly confirm that RFR-induced increases in hypothalamic temperature of about 0.3 deg C in the squirrel monkey trigger behavioral thermoregulation and that other thermodetectors may also contribute, but that the processes involved are as yet speculative.

It may be significant to emphasize that hypothalamic temperature rises were evident at all of the subthreshold power densities used (mentioned above). Specifically at 4 mW/sq cm, the lowest level, the corresponding estimated whole-body SAR was only about 0.6 W/kg. Obviously the local SAR in the hypothalamus was considerably higher, as noted by the

thors (citing Kritikos and Schwan, 1979). However, the absence of
havioral thermoregulation indicates that exposure at such whole-body
Rs is well within the capabilities of the autonomic thermoregulatory
stem of that primate species.

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'HOR ABSTRACT: Isolated sciatic nerves of frogs were exposed to 2.45-
: pulse-microwave radiation in a waveguide exposure system at an
:rage specific absorption rate (SAR) of 10 mW/g. In previous studies
ing continuous-wave (cw) microwave radiation at an SAR of 10 mW/g,
rvival time of the irradiated nerve when stimulated to fire at a high
te (50 twin pulses per sec) was shortened significantly. This
vestigation was performed to determine if pulse-microwave radiation
oduced the same or different effects on the vitality of frog sciatic
rves as continuous-wave microwave radiation.

ree sets of experiments were carried out using 10-microsecond-wide
lses at 50 pps, with an average SAR of 10 mW/g: (1) asynchronous
lsing wherein the mw pulse was delivered at varying times in the
ring cycle; (2) synchronous pulsing during the peak of the nerve
tion potential; and (3) synchronous pulsing during the quiescent
riod between nerve firings. In all three cases a significant decrease
the survival time of the exposed nerves, as compared to their
exposed mates, was seen. However, the magnitude of this effect was
sentially the same in all three cases and was also comparable with the
fect seen earlier using cw (of equivalent SAR).

udy Type: Nervous System; IN-VITRO; FROG
fect Type: Alterations in vitality of isolated sciatic nerves by
:posure to RFR pulses delivered asynchronously or synchronously
:lative to the firing rate stimulated with current pulses
equency: 2.45 GHz
dulation: 10-microsecond pulses at 50 pps (0.0005 duty cycle)
wer Density: Not measured
.R: 10 W/kg Av; 20 kW/kg Pk

:POSURE CONDITIONS: Exposures were done from below in a system
:scribed in McRee and Wachtel (1980), which was a modified version of
ie used by Chou and Guy (1978). A vertical section of waveguide
is sealed at the bottom with a quarter-wavelength dielectric slab and
.lled with frog Ringer's solution to a height of 10 cm; the slab was
ied to match the impedance of the solution to that of the air below.
io thin-wall polyethylene tubes 2 mm in diameter were placed across the
:nterline of the waveguide, presumably in the orientation parallel to
ie electric vector of the TE10 mode. One of the tubes was located in
'oximity to the slab; the other was positioned 5 cm above the slab
irface, where the intensity of the RFR was negligible because of the
:tenuation by the solution.

sealed during each experiment, it is not known whether changes in the Ringer's solution within the tubes (e.g., decreases in nutrients) were of sufficient magnitude to have also contributed to the variability observed.

The findings of this study appear to be contrary to the negative results reported by Chou and Guy (1978) for exposure of isolated nerves from the frog, cat, and rabbit to CW and pulsed 2.45-GHz RFR. However, Chou and Guy did not present any data for the frog. Also, McRee and Wachtel (1982) reported obtaining decreases in vitality of the frog sciatic nerve exposed to pulsed 2.45-GHz RFR at an average SAR of 10 W/kg that were comparable to the results with CW RFR at 10 W/kg in this study.

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MCREE
WACHTEL

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CELLULAR
CW
EXPOSURE-SYSTEM
FROG
IN-VITRO
NERVOUS-SYSTEM
RFR
THRESHOLD

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1980
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statement that there were no significant differences in CAP decay time at this SAR or their suggestion that the effects seen in the first series were not due to temperature differences.

The presentation of the decay ratio for each nerve in the two series (reproduced above from Tables I and II) permitted not only checking the means but also calculation of the standard deviations (SDs) thereof (not given in the paper). Surprisingly, the means shown in Table I were in error. The correct means (and SDs) for the first and second CAPs at 100 W/kg are 0.84 +/- 0.21 and 0.48 +/- 0.25; those at 50 W/kg are 0.65 +/- 0.28 and 0.63 +/- 0.24; and those for 20 W/kg are 0.84 +/- 0.18 and 0.71 +/- 0.22. Evidently there were considerable variations among the individual results for each SAR, which were therefore non-RFR-related. Dose-dependency was tested with the 1-tailed t-test, which showed that the differences among the first-CAP means for 100, 50, and 20 W/kg were statistically nonsignificant (p>0.05). This was also true for the second CAPs.

Thus, the authors were correct in stating that the exposed nerves decayed faster than the control nerves (all corrected ratios were less than unity) and that no dose dependence could be discerned for the first CAP. However, even though the second-CAP means did increase with decreasing SAR as noted by the authors, the evidence for dose-dependent changes for the second CAP was weak because these differences were also nonsignificant. (Perhaps a more sophisticated statistical method should be used to determine whether the trend was significant.)

In the second series, the mean and SD for the first-CAP ratios at 0 W/kg (3 experiments) were 1.24 +/- 0.15; the values for the second CAP were 1.20 +/- 0.32. The corresponding first-CAP values at 5 W/kg (4 experiments) were 1.24 +/- 0.49; the values for the second CAP were 1.02 +/- 0.25. At 10 W/kg (4 experiments), the first-CAP values were 0.52 +/- 0.20; the second-CAP values were 0.41 +/- 0.17. Thus, the mean ratios in Table II were correct.

It is interesting that the first-CAP means for 0 and 5 W/kg were both larger than unity (1.24), indicating that the control nerves decayed faster than the exposed nerves; however, the ratio at 10 W/kg was less than unity (0.52) and the difference was significant. Also, the second-CAP mean was larger than unity at 0 W/kg, about unity at 5 W/kg, and less than unity at 10 W/kg; the difference between the means for 0 and 5 W/kg was not significant, but the means for 5 and 10 W/kg did differ from each other significantly. Thus, these results support the existence of a threshold between 5 and 10 W/kg. However, the occurrence of ratios larger than unity indicates that uncontrolled non-RFR factors were present (ascribed by the authors to "natural variability of living nerves"), so repetition of the experiments with larger numbers of (and perhaps better-matched) specimens would be desirable.

The use of the polyethylene tubes filled with Ringer's solution to isolate the preparations from possibly toxic ions in the waveguide solution appears to be a worthy idea. However, since the tubes were

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1.00, 0.67, 1.00, and 0.70 for the first CAP, with a mean of 0.82, and
0.59, 0.50, 1.00, and 0.74 for the second CAP, with a mean of 0.66.

The authors stated: "The times for the CAPs of the exposed nerves to
decay to half amplitude for all SARs ... were less than for the CAPs of
the unexposed nerves. Although no clear dose-response relationship
could be detected for the first CAP decay, a faster decrease in
amplitude of the second CAP did occur with increasing dose (SAR)."

No results were presented for the experiments performed in which the IR
source was used to simulate the 100-W/kg temperature profile (described
previously), but the authors indicated that there was no significant
difference in decay time of the CAPs between the hotter (top) and the
cooler (bottom) nerve. They therefore suggested that the CAP decay-time
differences obtained with RFR in the first series were not due to the
temperature differences but were "specific to the microwave radiation".
In their discussion, however, they stated: "Although elevating the
temperature of the nerve did not have the same effect on vitality as
microwaves, the conclusion that the effect on vitality is microwave
specific does not preclude the possibility that nonuniform, localized
heating or thermal gradients inside the nerves are the mechanisms
producing the effect."

The authors indicated that two experiments of the second series were
done at 20 W/kg and stated (without presenting data) that the results
were basically the same as those of the first series at 20 W/kg. For
this reason, no higher SARs were used in the second series. The CAP
half-decay ratios obtained in the second series were presented in Table
II for SARs of 0, 5, and 10 W/kg. At 0 W/kg (3 experiments), the ratios
for the first CAPs were 1.40, 1.21, and 1.11 for a mean of 1.24; the
corresponding values for the second CAP were 1.57, 1.00, and 1.04 for a
mean of 1.20. At 5 W/kg (4 experiments), the values for the first CAP
were 1.21, 0.75, 1.91 and 1.07, with a mean of 1.24; the values for the
second CAP were 1.19, 0.68, 0.97, and 1.22, with a mean of 1.02. At 10
W/kg (4 experiments), the first-CAP values were 0.64, 0.35, 0.36, and
0.74 for a mean of 0.52; the second-CAP values were 0.50, 0.55, 0.40,
and 0.17 for a mean of 0.41.

The authors noted that in all four experiments at 10 W/kg, the CAPs of
the exposed nerve decayed faster than the control nerve. However, the
results at 0 and 5 W/kg were equivocal, i.e., the control nerve decayed
faster than the exposed nerve in some experiments. Such results were
ascribed to the natural variability among living nerves.

In their discussion, the authors concluded that the threshold for this
RFR effect was between 5 and 10 W/kg, and that the effect was not
reversible, since on termination of exposure, the nerves did not
revitalize or increase their activity above that at the end of exposure.

CRITIQUE: Since the only SAR overlap between the two series of
experiments was at 20 W/kg, it is unfortunate that the authors had not
presented any second-series data at 20 W/kg to substantiate their

exposed nerve was higher than for the control nerve at each SAR, with a difference of about 0.5 deg C at 100 W/kg. Experiments were also performed in which an infrared (IR) source was used to heat the control nerve (in the absence of RFR), with a view toward obtaining the same differential level as that with RFR (but with the top nerve hotter than the bottom one). The results indicated that a reasonable simulation of the 100-W/kg profile had been achieved for the upper nerve.

In this series, the stimulation magnitude of the pulse pair was set to yield a maximal CAP for the first pulse and one of half-maximal size for the second pulse. A representative result at 50 W/kg was displayed. After 5 min of exposure, the amplitudes of the first and second CAPs for the exposed nerve were slightly smaller than the corresponding values for the control nerve, with some minor shape differences discernible. After 43 min, the CAPs of the control nerve had diminished slightly (retaining the 2:1 ratio between first and second amplitudes) but the CAPs of the exposed nerve had diminished much more. At 55 min, further diminution of the CAPs of the control nerve had occurred but those of the exposed nerve were barely discernible on the scale used.

In the second series of experiments, the Ringer's solution within the waveguide was circulated through a temperature-controlled water bath. In this manner, the exposed and control nerves were maintained at 24 +/- 0.05 deg C for all SARs. The stimulus amplitude was set to produce maximal and equal first and second CAPs. Typical results after exposure for 2, 50, 105, and 172 min at 10 W/kg were presented. At 2 min, there was little difference between the first and second CAPs for either nerve or between the two nerves. At 50 min, the second CAP of the control nerve had diminished relative to its first CAP, indicating that the control nerve had lost some vitality. However, this effect was more pronounced for the exposed nerve. By 105 min, the first CAPs of both nerves and the second CAP of the control nerve had diminished, but the second CAP of the exposed nerve was no longer evident. By 172 min, the first and second CAPs of the control nerve had both decreased considerably, but both CAPs of the exposed nerve were absent.

To quantify such changes and to account for vitality changes in control nerves, the "half-decay time ratio" for each CAP was defined as the time necessary for the CAP of the exposed nerve to decrease to half its value, divided by the half-value time for the corresponding CAP of the control nerve. Thus, values of this ratio less than unity indicate that exposed nerve decayed faster than the control nerve, and vice versa for ratios larger than unity.

The results for the first series of experiments were presented in Table I for SARs of 100, 50, and 20 W/kg. For 100 W/kg (4 experiments), the ratios for the first CAP were 0.99, 0.56, 0.80, and 1.00, with a mean of 0.79; the corresponding values for the second CAP were 0.48, 0.35, 0.83, and 0.25, with a mean of 0.39. For 50 W/kg (6 experiments), the first-CAP values were 0.96, 0.82, 0.79, 0.23, 0.71, and 0.40, with a mean of 0.51; for the second CAP they were 0.79, 0.50, 0.86, 0.21, 0.78, and 0.61, with a mean of 0.49. For 20 W/kg (4 experiments), the values were

surface, where the intensity of the RFR was negligible because of the attenuation by the solution.

One of the sciatic nerves from each frog was pulled through the lower tube for exposure and its mate was pulled through the other tube as a control. Both tubes were filled with Ringer's solution. Stimulating electrodes were attached at one end of each nerve outside the waveguide and recording electrodes were attached at the opposite ends.

OTHER INFORMATION: The polyethylene tubes were used to preclude effects of toxic ions in the Ringer's solution and to prevent leakages that could shunt the electrodes. SARs of the Ringer's solution at the location of the lower nerve were calculated from measurements of net forward (input minus reflected) power, the cross-sectional area of the waveguide, and the density and attenuation constant of the solution. To determine whether the presence of the polyethylene tubes significantly altered the absorption characteristics of the solution, temperature-vs-time profiles were measured, during exposure at 100 W/kg for 60 min, with small glass-coated thermistors at locations within the tubes, just outside the tubes, and at the tube sites in their absence. The profile for the site next to the lower tube was slightly higher than for inside that tube, and the latter profile was slightly higher than for the site in the absence of the tube, but the differences were no greater than 0.1 deg C (at 100 W/kg). The differences among the profiles for the control tube were negligible.

As noted by the authors, for a short period after a nerve is stimulated to fire by a current pulse, it is relatively refractory (less responsive to a second pulse). Thus, in the absence of fatigue, presentation of two pulses spaced at an interval longer than the refractory period would yield two compound-action-potential (CAP) responses of the same shape and magnitude. However, as a nerve fatigues from repeated stimulatory activity, its refractory period increases. Therefore, the amplitudes of CAP responses to second pulses (second-CAP responses) spaced from their first pulses at an interval equal to the initial refractory period diminish with time relative to the amplitudes of the CAPs for the first pulses (first-CAP responses). For a healthy frog sciatic nerve, the refractory period is slightly longer than 5 ms. In this study, therefore, both nerves were stimulated with current-pulse pairs with a separation of 5 ms, so that the second pulse would occur at almost the end of the initial refractory period, thereby permitting observation of time changes of refractory period and loss of excitability.

At the beginning of each experiment, both nerves were stimulated for 10 min in the absence of RFR with pulse pairs at a repetition rate of 5 pairs per second (pps), which allowed the nerves to stabilize. The repetition rate was then increased to 50 pps, and RFR exposure at the desired SAR was begun.

In the first series of experiments, nerves were exposed at 100, 50, 20, and 0 W/kg for 60 min at each SAR without circulating the solution in the waveguide. As a consequence, the temperature-time profile for the

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McRee, D.I. and H. Wachtel
THE EFFECTS OF MICROWAVE RADIATION ON THE VITALITY OF ISOLATED FROG
SCIATIC NERVES

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AUTHOR ABSTRACT: Isolated frog sciatic nerves were exposed to 2.45-GHz
CW microwave radiation in a waveguide exposure system. The nerves were
exposed to specific absorption rates (SARs) ranging from 0 to 100 mW/g.
The effect of the microwaves on vitality of the nerves was measured in
terms of the ability of the nerves to sustain a high firing rate over
prolonged periods without suffering appreciable changes in the
characteristics of the compound action potential (CAP). The nerves were
stimulated using twin pulses separated by a 5-msec interval at a
repetition rate of 50 pulses/sec.

For SARs equal to or greater than 10 mW/g, the exposed nerves first
underwent a prolongation of their refractory period and, later in the
exposure, severe decreases in the maximal CAP. Although the time at
which changes began to occur differed in each pair of nerves due to
normal biological differences in nerves from different frogs, a
prolongation of their refractory period and decrease in the second CAP
usually were observable after 20 to 30 min of exposure. These effects
appear to be microwave specific since they occurred when temperature was
held constant but not when an increase in temperature without microwaves
was produced. The effects were also irreversible since the nerves did
not revitalize or increase their activity on termination of exposure.
No significant effects on vitality of the nerves were observed for an
SAR of 5 mW/g in this series of experiments.

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Study Type: Nervous System; Exposure Methods, Dosimetry, and Modeling;
IN VITRO; FROG
Effect Type: RFR-induced alterations of refractory periods and
compound-action-potential characteristics of isolated nerves
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not measured
SAR: 0, 5, 10, 20, 50, or 100 W/kg

EXPOSURE CONDITIONS: Exposures were done from below in a system similar
to that used by Chou and Guy (1978). A vertical section of waveguide
was sealed at the bottom with a quarter-wavelength dielectric slab and
filled with frog Ringer's solution to a height of 10 cm; the slab was
used to match the impedance of the solution to that of the air below.
Two thin-wall polyethylene tubes 2 mm in diameter were placed across the
centerline of the waveguide, presumably in the orientation parallel to
the electric vector of the TE10 mode. One of the tubes was located in
proximity to the slab; the other was positioned 5 cm above the slab

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CW
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tension might be produced by the fields per se (i.e., nonthermally) is negated by the absence of such effects at the SARs that yielded no measurable rises in solution temperature. On the other hand, the positive results at the SARs that increased the solution temperature were clearly thermal, as evidenced by their replication with non-RFR means, but this conclusion could have been reinforced at such SARs by the use of a more effective circulation system. It is also likely that the preparations were heated by contact with the fluid rather than by RFR absorption, because these results were insensitive to the orientation of the preparations relative to the E-vector.

The numbers of nerve and muscle preparations of each type studied were not indicated. Presumably the single results presented for each type were representative, but they provided no indication of how reproducible such results were. Notably absent were representative results for the frog sciatic nerve. In two subsequent investigations, McRee and Wachtel (1980, 1982) exposed isolated frog sciatic nerves to 2.45-GHz CW- and pulsed RFR at an average SAR of 10 W/kg in a similar waveguide system, and reported that the survival time of nerves stimulated to fire at a high rate was shortened significantly as compared with control nerves.

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In FUNDAMENTAL AND APPLIED ASPECTS OF NONIONIZING RADIATION, Plenum Press, N.Y., pp. 93-127 (1975)

section about 4 sq cm of the sternocostal portion of the muscle was dissected in Ringer's solution. Strings sutured on the central tendon and residual intercostal muscles were pulled through small opposing holes on the narrower walls of the waveguide. Two Plexiglas chambers attached to the exterior waveguide walls served to support the muscle under tension, and a third provided an access port for stimulating the phrenic nerve. The muscle was fixed at one end and connected to the tension transducer near the other end by the strings.

Current pulses 0.3 ms in width and 0.3-30 mA in amplitude were applied to the phrenic nerve once every 5 seconds for single-twitch experiments and 15-30 per second for tetanus experiments. The muscles were exposed to the pulsed or CW RFR at each SAR for 5 min, with intervals of 5-10 min between exposures.

A transient-averaging computer was used to obtain plots of mean tension vs time for 10 single twitches. The mean single-twitch tension for a muscle before, during, and after exposure to 1-microsecond pulses (1000 pps) at 220 kW/kg peak and to CW at 1500 W/kg were displayed in Fig. 8. The pulsed RFR increased the solution temperature 0.2 deg C, but had little effect on twitch tension. With the CW RFR, the solution temperature increased by 1 deg C, which was accompanied by a decrease in tension amplitude and a reduction of latency time. The postexposure values of tension amplitude and latency time were even smaller. However, these exposure and postexposure results were replicated by a non-RFR-induced solution-temperature increase of 1 deg C.

Plots of mean tetanus tension for a muscle stimulated with 0.3-ms, 30-mA pulses at 15 pps and exposed to maximum pulsed and CW SARs (220 kW/kg and 1500 W/kg) during the decreasing phase of tetanic contraction were displayed in Fig. 9. No RFR-induced changes were evident. Tests to determine whether the RFR at these SARs directly altered the tension of muscles not stimulated with current pulses also yielded no effects.

In their discussion, the authors noted that their negative results at SARs that did not increase the solution temperature were at variance with those of Kamenskii (1964, 1968), Rothmeier (1970), and Portela et al. (1975). However, the nerve preparations of Kamenskii and Rothmeier were exposed to RFR in air, so the SARs could have been high even though the incident power densities were low.

The authors also indicated that their negative findings without current-pulse stimulation do not support the hypothesis of direct neural stimulation proposed by Frey (1971) as the basis for the RFR-auditory effect or that RFR causes neurotransmitter release in isolated turtle hearts by excitation of nerve remnants therein (Tinney et al., 1976).

CRITIQUE: It is important to emphasize that the RFR fields were present within the preparations irrespective of their temperature equilibration with the Ringer's solution, i.e., even when the capabilities of the circulation system were adequate to avoid discernible temperature rises therein. Thus, a hypothesis that changes in neural CAPs or muscle

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deg C.

Specimens were also exposed to pulsed RFR at 220 kW/kg peak SAR (220 W/kg average SAR) and to CW RFR at 1500 W/kg in the absence of current-pulse stimulation to test for the possibility of direct RFR stimulation.

For exposures of the stimulated preparations to pulsed or CW RFR in either orientation relative to the E vector at SARs that did not increase the fluid temperature near the center of the specimen, no changes in either amplitude or conduction velocity of the CAP were observed. At the SARs that increased the fluid temperature by 1 deg C, a slight increase in conduction velocity was obtained. Data supporting the latter finding were presented in Figs. 5-7. The conduction velocity and peak CAP amplitude vs time were shown in Fig. 5 for a cat saphenous nerve exposed to CW RFR at 1500 W/kg parallel to the E-vector. During exposure, the temperature increased by 1 deg C and the conduction velocity increased by about 2%, but the amplitude variations displayed were small and apparently not RFR-dependent. The increase of conduction velocity was reproduced by raising the temperature of the solution by non-RFR means.

Figure 6 showed CAP recordings for a stimulated rabbit vagus nerve before, during, and after exposure to 10-microsecond pulses (100 pps) at 220 kW/kg peak, and to CW RFR at 1500 W/kg, with the nerve perpendicular to the E-vector. For the pulsed-RFR case, the solution temperature rose 0.3 deg C, which increased the conduction velocity slightly (from 117 to 118 m/s). For the CW case, the solution-temperature rise was 1 deg C, which increased the conduction velocity from 117 to 135 m/s. In addition, an equivalent rise in solution temperature produced by non-RFR means yielded the same velocity increase.

The CAP recordings for a rabbit superior cervical ganglion mounted at right angles to the E-vector and exposed to 1-microsecond pulses (1000 pps) and to CW RFR at the same SARs as the vagus nerve were shown in Fig. 7. For the pulsed RFR, the solution-temperature rise was 0.3 deg C as before, but the latency time, 17 ms, remained unchanged. The temperature increase produced by the CW RFR was again 1 deg C, and the latency time decreased to 16 ms, a result reproduced by increasing the solution temperature 1 deg C by non-RFR means.

In the absence of current-pulse stimulation, no direct stimulatory effects of exposure were observed at the highest available SARs (pulsed RFR at 220 kW/kg peak or CW RFR at 1500 W/kg).

The effects of RFR on contraction of rat diaphragm muscle were studied by means of a tension transducer designed so that during contraction, a shutter between a light-emitting diode and a photoresistor would alter the transmission of infrared light from the diode to the resistor and hence the voltage across the resistor in proportion to the tension.

Diaphragm muscle with right and left phrenic nerves were excised and a

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the waveguide either parallel or perpendicular to the electric field of
the TE10 mode. The penetration depth of the solution (at 2.45 GHz) was
1.65 cm, so the 6-cm column of fluid was essentially equivalent to one
of infinite length.

OTHER INFORMATION: SARs of the Ringer's solution at the location of the
isolated specimen were calculated from values of net forward (input
minus reflected) power, the density of the solution, the cross-sectional
area of the waveguide, and the attenuation constant of the solution
derived from measurements of its dielectric constant and electrical
conductivity. Thin tissue preparations having dielectric properties
close to those of the solution would not significantly perturb the
fields within the solution. Thus, such calculated local SARs in the
solution would be applicable to the tissues as well. SARs were also
determined by measurements of temperature rises with nonperturbing
probes. Because of the rapid heat convection of Ringer's solution, the
preparations were embedded in a jelly simulation of Ringer's solution.
The results were in reasonable agreement with the calculated values
(about 10% lower than the latter, possibly due to differences in the
properties of the simulated and actual Ringer's solutions).

Possible RFR effects on frog-sciatic and cat-saphenous nerves, which
contain mainly myelinated nerves, and on the rabbit vagus nerve, which
consists of both myelinated and unmyelinated fibers, were considered.
In addition, effects were sought on the superior cervical ganglion (of
the rabbit) because it contains not only neuron cell bodies but also
numerous synaptic junctions at which acetylcholine and norepinephrine
are released.

Each vagus nerve or superior cervical ganglion was mounted within the
waveguide (parallel or perpendicular to the E-vector), with one end
passing through an appropriate hole in the waveguide wall to a pair of
stimulation electrodes and the other end through the opposing hole to
recording electrodes. Each specimen was stimulated with a 0.3-
millisecond current pulse of 0.3-30 mA at 2-second intervals before,
during, and after RFR exposure; the compound action potentials (CAPs)
were recorded; and their conduction velocity and amplitude were
determined.

The vagus nerves were exposed to 1-microsecond RFR pulses at 1000 pps or
to 10-microsecond pulses at 100 pps for 10-min periods at average SARs
of 0.3, 3, 30, and 220 W/kg or to CW RFR at the same SARs, with 5 min
between exposures. Exposures of the superior cervical ganglia were only
for 5-min periods because of their shorter lifetimes. During exposure,
the temperature of the solution at the fluid outlet of the waveguide
section was held constant at 37 +/- 0.02 deg C. However, the fluid
temperature at the center of the mounted specimen (measured with a
nonperturbing temperature probe) rose by as much as 1 deg C during
exposure because of the limited pumping rate of the circulator. Frog-
sciatic and cat-saphenous nerves were studied in similar fashion, except
that the frog preparations were immersed in amphibian Ringer's solution
held at room temperature instead of mammalian Ringer's solution at 37

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Chou, C.-K. and A.W. Guy
EFFECTS OF ELECTROMAGNETIC FIELDS ON ISOLATED NERVE AND MUSCLE
PREPARATIONS

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AUTHOR ABSTRACT: An S-band waveguide exposure system was designed to
study the electromagnetic fields on the isolated tissues. The
temperature of the exposed tissue was maintained at a constant
temperature by circulating temperature controlled Ringer's solution
through the waveguide. Isolated frog sciatic nerves, cat saphenous
nerves, rabbit vagus nerves and superior cervical ganglia, as well as
rat diaphragm muscles were placed in the waveguide either parallel or
perpendicular to the electric field of the TE10 mode. Compound action
potentials of nerves or contractile tensions of muscles were recorded
before, during and after the 2450-MHz microwave irradiation.

Results showed no significant change in characteristics of nerves or
muscles exposed to CW specific absorption rate (SAR) of 0.3-1500 W/kg
and pulsed peak SAR of 0.3-220 kW/kg. The effects observed during
high-power radiation were reproducible by changing the solution
temperature. No direct field stimulation of nerves or muscles was
observed during microwave irradiation.

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Study Type: Nervous System; Exposure Methods, Dosimetry, and Modeling;
IN VITRO; FROG, CAT, RABBIT, RAT
Effect Type: RFR-induced alterations of compound action potential of
isolated frog sciatic nerves, cat saphenous nerves, rabbit vagus nerves,
and rabbit superior cervical ganglia, and of contractile tension of rat
diaphragm muscles
Frequency: 2.45 GHz
Modulation: CW; 1-microsecond pulses at 1000 pps or 10-microsecond
pulses at 100 pps (0.001 duty cycle)
Power Density: Not measured
SAR: 0.3-1500 W/kg CW; 0.3-220 W/kg Av, 0.3-220 kW/kg Pk pulsed

EXPOSURE CONDITIONS: Exposures were done from below in a vertical
section of rectangular waveguide (inside dimensions 7.2 cm x 3.4 cm)
filled with Ringer's solution to a height of 6 cm. A quarter-wavelength
dielectric slab was used to match the impedance of the solution to that
of air and to seal the bottom of the section. The solution was
maintained at constant temperature by a circulation system connected to
inlet and outlet ports through the walls at the bottom of the section.
Holes 3 mm in diameter were drilled in the four walls 1 cm above the
slab, and Plexiglas chambers were glued to the outside walls against
each hole. The chambers served to hold stimulating and recording
electrodes for isolated tissue specimens mounted across the center of

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One of the sciatic nerves from each frog was pulled through the lower tube for exposure and its mate was pulled through the upper tube as a control. Both tubes were filled with Ringer's solution. Stimulating electrodes were attached at one end of each nerve outside the waveguide and recording electrodes were attached at the opposite ends.

OTHER INFORMATION: As discussed in McRee and Wachtel (1980), field perturbation by the presence of the polyethylene tubes was found to be insignificant. The average SAR of the Ringer's solution at the location of the lower nerve was determined from measurements of net forward (input minus reflected) power, the waveguide's cross-sectional area, and the density and attenuation constant of the solution. Verification was obtained from time-temperature profiles measured with a noninteracting temperature probe.

As noted by the authors, for a short period after a nerve is stimulated to fire by a current pulse, it is relatively refractory (less responsive to a second pulse). Thus, in the absence of fatigue, presentation of two pulses spaced at an interval longer than the refractory period would yield two compound-action-potential (CAP) responses of the same shape and magnitude. However, as a nerve fatigues from repeated stimulatory activity, its refractory period increases. Therefore, the amplitudes of CAP responses to second pulses (second-CAP responses) spaced from their first pulses at an interval equal to the initial refractory period diminish with time relative to the amplitudes of the CAPs for the first pulses (first-CAP responses). For a healthy frog sciatic nerve, the refractory period is slightly longer than 5 ms. In this study (as in the previous one), therefore, both nerves were stimulated with current-pulse pairs with a separation of 5 ms, so that the second pulse would occur at almost the end of the initial refractory period, thereby permitting observation of time changes of refractory period and loss of excitability.

In this study, the magnitude of the stimulus was set such that the initial first and second CAPs were maximal and approximately equal in magnitude. At the start of each experiment, both nerves were stimulated for 10 min in the absence of RFR with pulse pairs at a repetition rate of 5 pairs per second, which allowed the nerves to stabilize. The repetition rate was then increased to 50 pairs per second (i.e., twin-pulse stimulation was done at 20-ms intervals) and RFR exposure at an average SAR of 10 W/kg was begun. The 10-microsecond RFR pulses were also delivered at 50 pulses per second (20-ms intervals).

In one set of experiments, the RFR pulses were delivered in synchrony with the peak of the CAP. In another set, the RFR pulses were arranged to arrive during the 15-ms quiescent intervals between successive 5-ms twin-pulse stimulations. In still another set, the RFR pulses were made to arrive asynchronously during the 5-ms stimulation intervals, i.e., at varying times within those intervals.

The authors did not present any representative CAP recordings, but they described the results qualitatively as follows: "During exposure the

exposed nerves first underwent a prolongation of their refractory period as evidenced by a decrease in amplitude of the second CAP. This prolongation of the refractory period and decrease in the second CAP usually were observable after 20 to 30 min of exposure. Later in the exposure, severe decreases in maximal CAP amplitude occurred. During the same periods the control nerves showed little change in these characteristics."

To quantify RFR-induced effects on CAPs and to account for vitality changes in control nerves, the authors defined the "half-decay time ratio" for each CAP as the time necessary for the CAP of the exposed nerve to decrease to half its value, divided by the half-value time for the corresponding CAP of the control nerve. Thus, values of this ratio less than unity indicate that the vitality of the exposed nerve decayed faster than for the control nerve, and vice versa for ratios larger than unity.

The half-decay-time ratios for the first and second CAPs derived from 5 experiments with RFR pulses delivered synchronously with the peak of the CAP were presented in Table I of the paper. All 10 individual ratios were less than unity, indicating that both the first and second CAP of each exposed nerve had decayed faster than its control nerve. The means and standard deviations (SDs) for the first and second CAPs were stated to be 0.58 +/- 0.25 and 0.59 +/- 0.14, respectively. However, the individual ratios shown were used to verify the means and SDs; the correct value for the first-CAP mean was found to be 0.48.

The mean first- and second-CAP ratios and SDs for the 5 experiments with synchronous RFR pulses out of phase with the peak of the CAP were 0.66 +/- 0.21 and 0.65 +/- 0.07, respectively (Table II). The values for the 6 experiments with asynchronous RFR pulses were 0.50 +/- 0.21 and 0.69 +/- 0.21 (Table III). (No errors of consequence were found in either table.) In both sets of experiments, all the ratios were also less than unity.

The authors stated that statistical examination of the data by both analysis of variance and the 2-tailed t-test showed that the vitality loss of the exposed nerve was highly significant (p<0.01) relative to that of the control nerve, but that there were no significant RFR-phase-related differences among the results.

CRITIQUE: In the absence of numerical results of the statistical analyses, little comment can be offered regarding the degree of validity of the findings except to indicate that perhaps the authors should have used the 1-tailed instead of the 2-tailed t-test, because the predicted outcome was unidirectional (loss of nerve vitality).

The less-than-unity half-decay time ratios displayed in the three tables of the paper clearly indicate that the vitality of every exposed nerve, as assessed from the first and second CAPs separately, diminished more rapidly than that of its control nerve. Not clear, however, is the interpretation of the observation that some of the second-CAP ratios

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were larger than their corresponding first-CAP ratios. For example, the first-CAP and second-CAP ratios obtained in one of the experiments with RFR pulses at the peak of the CAP response were respectively 0.35 and 0.60 (Table I). One possible interpretation of this result is that the second-CAP time of the control nerve had not changed materially relative to its first-CAP time (as befits an adequate control) and that the second-CAP time of the exposed nerve had increased about 71% relative to its first-CAP time, a biologically unlikely result. A more tenable interpretation is that the second-CAP time of the control nerve had decreased materially while that of the exposed nerve also had decreased, but less so. If this was the case, then there were uncontrolled non-RFR factors present in the experiment.

The case above is not unique. Specifically, the second-CAP mean half-decay-time ratio for that set of experiments (0.59) was 23% larger than the (corrected) first-CAP mean (0.48); also, the first- and second-CAP means shown in Table III were 0.50 and 0.69, respectively.

In this context, it is interesting that for the study with CW RFR (McRee and Wachtel, 1980), there were a few isolated cases similar to those above, but all of the second-CAP means were smaller than their corresponding first-CAP means.

Although Chou and Guy (1978) reported negative results for exposure of isolated frog sciatic nerves (and preparations from other species) to CW and pulsed 2.45-GHz RFR, they did not present any data for the frog, so comparisons cannot be made.

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PREPARATIONS
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THE EFFECTS OF MICROWAVE RADIATION ON THE VITALITY OF ISOLATED FROG
SCIATIC NERVES
Radiat. Res., Vol. 82, pp. 536-546 (1980)

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Ashani, Y., F.H. Henry, and G.N. Catravas
COMBINED EFFECTS OF ANTICHOLINESTERASE DRUGS AND LOW-LEVEL MICROWAVE
RADIATION

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AUTHOR ABSTRACT: Rats administered an anticholinesterase drug
(phospholine iodide) and exposed 10 min later to a pulsed microwave
irradiation with an average power density of 10 mW/sq cm for 10 min
showed a statistically significant decrease in body temperature when
compared to various control groups. The enhancement of hypothermia in
the presence of low-level microwave irradiation was also observed when
rats were injected with another powerful inhibitor of acetylcholinester-
ase, paraoxon, and with 2-pyridine aldoxime methyl methanesulfonate, an
antidote against anticholinesterase poisoning. The effect from the
combination of microwave and anticholinesterase drugs may potentially be
used as a tool to study effects of low-power density microwave fields on
biological systems.

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Study Type: Nervous System, Multiagent Interactions, Physiology and
Biochemistry; IN VIVO; RAT
Effect Type: Effects of RFR on the hypothermia induced by
anticholinesterase drugs and their antidotes
Frequency: 2.8 GHz
Modulation: 2-microsecond pulses at 500 pps (0.001 duty cycle)
Power Density: 10 mW/sq cm Av
SAR: Not determined

EXPOSURE CONDITIONS: Exposures were done in an anechoic chamber used by
Thomas et al. (1979). Each rat was suspended in a plastic mesh sleeve
and exposed to 2-microsecond pulses at 500 pulses per second for 10 min
at a distance of 40 cm (near field) from the mouth of a standard-gain
horn. The long axis of the rat was transverse to the propagation
direction. In the study by Thomas et al. (1979), the electric vector
was vertical. Presumably, this was the case in this study as well. The
average power density was 10 mW/sq cm. For some experiments, the
temperature in the chamber was not controlled and it averaged 25 +/- 3
deg C during exposure; for others, it was held at 10 deg C for specified
periods.

OTHER INFORMATION: Adult male rats, each weighing 250-380 g, were
divided into three treatment groups. Group A was subcutaneously
injected with 0.05-0.12 ml of the anticholinesterase drug phospholine
(iodide) at doses of 0.030, 0.040, 0.045, 0.050 or 0.055 mg/kg and sham-
exposed; Group B was given phospholine (same doses), followed 10 min
later by exposure to the RFR; and Group C was given phospholine (same
doses) 3 min after exposure to RFR. Core temperatures were measured
prior to drug injection, just after exposure, and at various subsequent

intervals, using a clinical thermometer or thermistor inserted 6 cm into the colon.

Prior to and following treatment, some rats of each group were kept in standard cages (two per cage) at 25-26 deg C, with food and water available ad libitum, and their core temperatures were measured at 40-min intervals for 240 min after treatment. Other rats were similarly housed and measured, but the ambient temperature was lowered to 10 deg C during post-treatment time intervals 80-140 min and 260-320 min. (Such alterations of ambient temperature were used to enhance any treatment-induced hypothermia.) Control rats for each treatment group were given saline instead of phospholine.

Mean core temperatures taken 90 min after treatment (without reduction of ambient temperature) were plotted vs dose for the three treatments. The means for Group A, estimated from the plotted points, were 38.5, 38.4, 38.0, 37.8, and 37.1 deg C respectively for the five doses in increasing order. The corresponding values for Group B were 38.5, 37.8, 37.3, 37.3, and 37.0 deg C. Thus, the largest differences in core temperatures occurred for the intermediate doses of the drug, indicating the possible existence of a drug-dose "window" for most effective RFR interaction. The temperatures for Group C were 38.3, 37.8, 38.1, 37.6, and 36.7 deg C, which were comparable to those for Group A.

T-test analysis of the dependence of core temperature on dose for Group A showed that the mean temperatures for 0.030-0.045 mg/kg did not differ significantly from one another, but that the differences for 0.045-0.055 mg/kg were significant ($p < 0.01$). Group C yielded similar results. For Group B, however, the differences in temperatures for 0.030-0.045 mg/kg were significant ($p < 0.001$), as well as those for 0.045-0.055 ($p < 0.04$). Thus, all three groups suffered progressive hypothermia with increasing dose, but the effect was more severe for Group B than either Group A or C, which did not differ significantly from each other.

Plots of mean core temperature vs time for sham-exposed, saline-control rats held at 25-26 deg C during the entire post-treatment test period showed a value of 38.8 deg C at 0 min (immediately after treatment), a drop to 38.3 at 40 min, and minor variations from the latter at subsequent times. The temperature of the sham-exposed, saline-control rats subjected to the periods of lower ambient temperature dropped to 38.1 deg C at 40 min, but the results were otherwise similar. Regarding comparative results with RFR, the authors stated (without presenting data): "The same profiles were recorded for irradiated and nonirradiated rats that did not receive the anticholinesterase drug." They also noted that all the rats (> 200) in this study exhibited relatively high initial core temperatures, which they ascribed to the stress imposed during preliminary handling and temperature measurement.

To ascertain the origin of the hypothermia induced by phospholine, some unexposed rats were injected i.p. with 0.022 mmole/kg of atropine sulfate or atropine methyl nitrate (both antidotes for phospholine) or with saline 5 min prior to injection of 0.045 mg/kg of phospholine. The

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core temperatures of the rats were measured for 3 hr under an ambient temperature of 25-26 deg C during the first hr, 10 deg C for the next hr, and 25-26 deg C for the remaining hr. All the rats had an initial core temperature of 38.8 deg C. The mean temperatures of the saline controls at 1, 2, and 3 hr post-treatment were 37.6, 36.9, and 37.5 deg C, respectively; the corresponding values for the rats given atropine sulfate were 38.4, 37.5, and 38.0 deg C; and the values for the rats given atropine methyl nitrate were 37.1, 36.4, and 36.8 deg C. Thus, the atropine sulfate reduced the phospholine-induced hypothermia and the atropine methyl nitrate enhanced it.

To determine the effects of the antidotes alone, other unexposed rats were injected with atropine sulfate or atropine methyl nitrate followed by saline instead of phospholine. The core temperatures obtained with the former were respectively 38.2, 38.0, and 37.6 deg C at 1, 2, and 3 hr. The corresponding values for atropine methyl nitrate were 37.9, 37.7, and 37.6 deg C. The temperature differences at corresponding times were smaller than for those with phospholine present. Thus, both antidotes induced hypothermia.

Groups of rats were subcutaneously injected with 0.2 mg/kg of another anticholinesterase drug, paraoxon, followed 10 min later by 10 min of RFR- or sham exposure. The mean core temperature of both groups dropped from 39.0 to about 36 deg C at 80 min, the start of the first 60-min interval at 10 deg C. At the end of that interval (140 min after treatment), the mean core temperature of the RFR-exposed rats dropped to 33.6 deg C as contrasted with 35.0 for the sham-exposed rats. The mean temperatures of both groups rose to 37.7 deg C at 260 min, the start of the second 60-min interval at 10 deg C, and decreased to 35.7 and 36.4 deg C for the RFR and sham groups, respectively, at the end of that interval. The difference in means at 140 min was significant ($p<0.02$). Thus, exposure to the RFR significantly enhanced the hypothermia induced by paraoxon, as was the case for phospholine.

Other groups of rats were injected i.p. with 50 mg/kg of 2-pyridine aldoxime methyl methanesulfonate (P2S), an antidote for paraoxon, and 10 min later were RFR- or sham-exposed for 10 min. The hypothermia shown by both groups was less pronounced than for paraoxon, but again the mean temperature for the RFR group at 140 min was significantly lower ($p<0.03$) than for the sham group.

In the final set of experiments, temperature profiles were obtained for groups of rats given P2S, exposed to the RFR for 10 min, and injected 10 min later with paraoxon. At 0 min (after paraoxon injection), the mean core temperature was 38.9 deg C for both groups, but the values for the RFR group were lower than those for the sham group at all corresponding subsequent times. Specifically, at 80 and 160 min, the start and end of the 10-deg-C interval, the core temperatures for the RFR group were 35.4 and 33.7 deg C, respectively, and the corresponding values for the sham group were 36.3 and 35.2 deg C. The values for the RFR group at 260 and 320 min, encompassing the second 10-deg-C interval, were 35.7 and 34.8, respectively, and those for the sham group were 36.7 and 36.2 deg C.

These differences were larger than those obtained with P2S not followed by injection with paraoxon.

In their discussion, the authors stated that: "Rats administered 0.045 mg/kg phospholine iodide developed slight poisoning symptoms such as fascisculations and tremors. Furthermore, peripheral inhibition of AChE induced possible changes in several physiological systems such as cardiovascular impairments. Therefore, it will be impossible to relate the observed combined effects on the hypothermia to a specific mechanism."

CRITIQUE: Since few people ingest anticholinesterase drugs or their antidotes, there appears to be no direct significance of the findings of this investigation with regard to possible effects of RFR on human health. On the other hand, the authors suggested that use of certain drugs in combination with RFR might enhance the effects of RFR, and therefore such use would serve as a tool for investigating effects of low-level RFR, by implication, in the absence of such drugs.

Most of the results of this study demonstrated the converse, that RFR enhanced the effects of the drugs used, with no clear evidence that such effects would occur with the RFR in the absence of the drugs. However, the authors noted that "P2S is a powerful reactivator of phosphorylated acetylcholinesterase and cannot penetrate the blood-brain barrier, presumably due to the presence of a positive charge on the aromatic quaternary nitrogen. We could show that low-level microwave irradiation of rats injected with 50 mg/kg P2S reduced significantly the body temperature compared to that of the nonirradiated control group that received the same dose of P2S." A possible interpretation of this finding is that exposure to the RFR increased the permeability of the BBB to P2S. However, as indicated by the authors, paraoxon readily passes through the BBB, so it seems unlikely that RFR alteration of the BBB was the primary mechanism for the positive findings with paraoxon.

A presentation by Ashani and Catravas (1980) contained much of the information in this paper, but gave greater emphasis to the role of the blood-brain barrier (BBB).

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ASHANI
HENRY
CATRAVAS

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BIOCHEMISTRY
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HYPOTHERMIA
IN-VIVO
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NERVOUS-SYSTEM
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AUTHOR ABSTRACT: Five experiments were performed on a total of 60
non-fertile eggs of Gallus gallus to determine the spatial character,
persistence, and physical basis of thermal gradients after a 300-s
exposure to the intense, multipath, 2.45-GHz yield of a multimode cavity
(dose rates: about 80 to 120 mW/g). After irradiation of an intact egg
that was first equilibrated to the ambient temperature, a 3-mm diameter
Plexiglas rod, which was fitted with junctions of four microwire
thermocouples at 10-mm intervals, was inserted to place the distal
junction in the approximate center of the yolk, the most proximal
junction in peripheral thin white.

Temperatures measured immediately after irradiation revealed a highly
reliable linear gradient of mean temperatures from central yolk to
peripheral white (P<0.001). The gradient was also highly persistent:
Mean temperatures of central yolk exceeded those of outer thin white by
more than 4 deg C 5 minutes after irradiation, and by more than 2 deg C
60 minutes afterward. In contrast, when an egg's contents were mixed
before irradiation, the gradient was effectively eliminated.

A previous report of athermally induced (field-specific) teratogenesis
in chick embryos is placed under an interpretive cloud by the present
findings: Terata emerged from eggs that were structurally intact during
microwave irradiation, but estimates of maxima of embryonic temperatures
were based on thermal measurements of non-fertile eggs the contents of
which had been mixed by a thermal probe BEFORE irradiation.

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Study Type: Teratology and Developmental Abnormalities; Exposure
Methods, Dosimetry, and Modeling; IN VITRO; CHICKEN
Effect Type: RFR-induced temperature gradients in intact unfertilized
eggs vs gradients in eggs mixed before exposure
Frequency: 2.45 GHz
Modulation: Mode-stirred amplitude modulation
Power Density: Not measured
SAR: 80-120 W/kg

EXPOSURE CONDITIONS: Groups of eggs initially stored at 5 deg C were
placed within an unenergized multimode cavity (Justesen et al., 1971)
for 3 hr, during which they were equilibrated to room temperature (20.7
+/- 2 deg C) by air flow at 0.5 m/s through the cavity. After
equilibration, a hole was drilled through the shell and outer shell-
membrane of each egg at the larger pole of the egg's long axis. The egg
was then weighed, enclosed in a thick-wall Styrofoam container, and

exposed to the RFR in the cavity for 300 seconds.

OTHER INFORMATION: The authors noted that the egg of the domestic chicken is a complex, multilayered, diffusion-resistant structure with a whole-body resonance close to 2.45 GHz, and that the center would be a region of maximum internal field ("hot spot") on the basis of both homogeneous models (Durney et al., 1978) and layered models (Barber et al., 1979). They also indicated that Van Ummersen (1961) had reported the occurrence of terata in chicken embryos exposed to 2.45-GHz RFR but had not found a central hot spot in temperature measurements at various depths in exposed unfertilized eggs. They questioned the validity of Van Ummersen's assumption that such temperature measurements would be representative of the temperature distribution in an intact egg, because the measurement technique used may have allowed significant mixing of the layers.

Experiment I was done to ascertain the temperature gradient within an egg immediately after intense RFR exposure. Calibration of energy deposition rate in an egg of representative mass was done with a phantom consisting of an eggshell that contained 50 g of distilled water. From temperature measurements in the phantom at various input powers to the cavity and by successive approximations, the cavity input power (value not stated) necessary to deposit energy in the egg at a rate of 4.0 W, corresponding to an SAR of 80 (+/- 17 SD) W/kg, was determined.

For temperature-gradient measurements within eggs, four copper-constantan microwire thermocouples were fastened onto a 3-mm diameter, 24-cm long, Plexiglas rod, one thermocouple at one end and the other three at 10-mm intervals therefrom. The thermocouples were calibrated by insertion of the assembly in a temperature-controlled water bath. Immediately after exposure of an egg, the rod was inserted through the hole in the larger pole of the egg's long axis so that the thermocouple junction farthest from the end of the rod barely penetrated into the outer thin white, just below the air sac. (Note that this thermocouple was labeled as the first in Figs. 2 and 3 but called the fourth in the text.) The criterion for proper rod placement was that yolk material be evident on the first 10 mm thereof. Three of the 22 eggs in experiment I failed this test and the results therefrom were excluded.

The mean temperatures for 19 eggs at depths of 0, 10, 20, and 30 mm were displayed in Fig. 3. The values and SDs estimated from the figure were respectively 30.7 +/- 2.2, 32.6 +/- 1.7, 34.6 +/- 2.3, and 36.5 +/- 2.8 deg C. By analysis of variance (the results of which were given in detail in Table 1 of the paper), the authors found that the gradient was linear with depth and highly reliable statistically. For comparison, the authors indicated that an egg probed after 3 hr within the unenergized cavity yielded a temperature at 30-mm depth that was 0.6 deg C lower than at the surface. There was some variation of mass among the eggs, with a mean of 51.7 (+/- 4.46 SD) g. To ascertain whether mass was a significant factor, the authors assigned the eggs to 3 groups (comprised of the 6 smallest, 6 intermediate, and 7 largest eggs), and performed a 3 (mass) x 4 (depth) analysis of variance. The results of

the analysis (given in Table 2 of the paper) indicated that the linear temperature gradient was not affected significantly by mass variation.

Experiment II was performed to determine the specific heats of egg white and yolk with a twin-well calorimeter. Comparisons were made of 100 g of egg yolk against 100 g of distilled water, each within a polyethylene bottle. The two bottles were equilibrated to 50 deg C by immersion for 1 hr in a circulating-water bath held constant at that temperature, which was 21.1 deg C above the internal temperature of the calorimeter. The bottles were then simultaneously removed, dried, and inserted into the calorimeter wells. The temperatures were recorded continuously for 24 hr afterward, and the area under each resulting curve was determined with a planimeter. Samples (100 g) of egg white vs water were similarly treated. The procedure was repeated 3 times for fresh yolk and 5 times for fresh white. The authors noted that: "No evident denaturing of yolk or white occurred at a temperature of 50 deg C, although the egg white was notably less viscous when removed from the calorimeter on the following day."

To determine the specific heat of each sample, the area under its curve was compared with that obtained from heating a precision resistor of known value in one well by passing a specified current for a specified time through the resistor. The accuracy of the calorimeter was verified by the use of a sample of mineral oil of known specific heat (0.5 cal/g) vs distilled deionized water (1.0 cal/g). The mean specific heats for yolk and white were found to be 0.747 and 0.893 cal/g, respectively. The authors noted that in the chicken egg, there are two whites in four layers, one (the thin white) of considerably lower viscosity than the other. For comparison, the values for yolk and white of the Japanese quail, found by Hamrick and McRee (1975), were 0.768 and 0.795 cal/g.

In experiment III, a measured quantity of homogenized and degassed egg white in a lavaged egg shell was exposed to the RFR eight successive times for 1 min each, with about 20 seconds between runs. After each exposure, the contents were stirred and a low-interference thermistor embedded in the cent.r of each egg was used to measure the temperature. The results were compared against those of an equal mass of water exposed in another shell. The temperature differences between white and water were averaged over the eight runs and used in the calorimetric equation to calculate energy and power levels. The same procedure was used for egg yolk. The authors stated that the results confirmed those obtained in experiment II (no data presented).

In experiment IV, eggs that were intact except for the hole in the shell were individually exposed to RFR for 300 seconds, 1 egg without thermal insulation and 7 thermally-insulated eggs. The energy-absorption rate used was 4 W for 7 eggs and 6 W for 1 egg. Just after exposure, the 4-thermocouple assembly was inserted and the temperatures were recorded for the 4 depths at: 1-min intervals for the first 20 min, 5-min intervals for the next 40 min, and 10-min intervals for 60 min more.

The authors stated (without presenting data) that the central yolk

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ooled at a rate slightly more than 0.03 deg C per min and that even fter the 2-hr period, the central yolk temperature was nearly 2 deg C igher than for the peripheral white.

lots of post-exposure temperature at each depth vs time for the hermally-insulated eggs were all reported to show rises to maxima uring the first few minutes, ascribed in part to the thermal capacity dded by the Plexiglas rod supporting the thermocouples and in part to he low thermal conductivities of near-intact yolk and white. In Fig. 4 f the paper, the cooling curves for a representative egg exposed at 4 W ere shown. The maxima ranged from about 31 deg C at the surface to bout 36 deg C at the center, with intermediate values for the other two epths. Beyond its maximum, the cooling curve for each depth was about inear with time, and the curves for the four depths were approximately arallel to one another. Plots of mean temperature vs time for the 6 ggs exposed at 4 W were shown in Fig. 6. The mean maxima ranged from bout 30 to 35 deg C. The cooling curves for the single egg exposed at W (Fig. 5) were similar except that the maxima ranged from 34 to 38 eg C.

n experiment V, cooling curves were obtained by the procedure used in he previous experiment, but for a lavaged shell filled with 56.0 g of ixed egg white alone or mixed egg yolk alone, and for the contents of a 9-g egg mixed before exposure by thrusting a 3-mm-diameter plastic rod epeatedly into a hole in the large end of the egg. After exposure at .0 W for 300 seconds, temperatures were measured at 1-min intervals for 0 min and at 10-min intervals for the next 110 min.

he authors indicated (without presenting data) that the temperature radients obtained for the shell filled only with white or yolk were uch smaller than, and were sometimes the reverse of, those for the ear-intact eggs. In addition, the thermal conductivity of each mixed onstituent was greater than when unmixed, as evidenced by the absence f the slow initial temperature rises toward maxima noted previously. he cooling curves for the egg with mixed contents were presented in ig. 7. These showed that immediately after exposure, the temperatures t the four depths were all about 38 deg C. (The authors noted that hese initial temperatures were intermediate between the extremes btained for the individual components.) In Fig. 7, the curves for epths 10 and 20 mm were almost coincident during about the first 40 in, and so were the curves for the surface and center, but the latter wo were lower than the former. For example, at 10 min after exposure, he temperature at the surface and the center were both about 34.6 deg , whereas those at 10 and 20 mm were both about 35.6 deg C. Beyond bout 40 min, all four curves were virtually coincident.

RITIQUE: Since an egg within a multimode cavity is exposed essentially rom all sides, its internal SAR distribution is considerably different han for exposure to plane-wave RFR (in any orientation). Also, the ole of whole-body resonance within a cavity is obscure. Nevertheless, xposure of an egg to 2.45-GHz RFR in such a cavity should yield maximal ocal SAR in the central region, in qualitative agreement with results

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ved from Durney et al. (1978) and Barber et al. (1979) for models
ised to plane-wave RFR. In this context, the mixed egg should have
orm RFR-absorption and thermal properties (unlike the intact egg,
which such properties of the various layers may differ significantly
ι one another).

data from experiment I were presented in detail (including results
)ossible sources of variation derived from the various statistical
lyses performed). Not understandable, therefore, was the total
ance of data from experiments II and III and the paucity of data from
other experiments. Inclusion of such data might have clarified
eral obscure aspects of the study, such as those discussed below.

ugh not explicitly stated, presumably each egg was removed from the
rofoam container after RFR exposure, and the temperature data were
en while the surface of the egg was directly exposed to ambient
perature. (Otherwise the cooling curves would be dependent on the
rmal characteristics of the Styrofoam container.) However, not clear
e the quantitative effects of the variations of ambient temperature
ı.7 +/- 2 deg C, see EXPOSURE CONDITIONS) on the cooling curves.

expected, experiment I yielded significant temperature gradients in
: near-intact eggs, with the center hotter than the surface. However,
: quantitative aspects of this and perhaps other experiments involving
)osure of near-intact eggs are open to question because the internal
nperature of each egg at the start of exposure may not have been
lform, as implicitly assumed. Support for this point is the authors'
servation that the central temperature of an egg after 3 hr within the
energized cavity was 0.6 deg C lower than its surface temperature.
esumably, the 3-hr period was not sufficient for the egg to fully
illibrate to room temperature (20.7 deg C) from its storage at 5 deg C
lor to insertion in the cavity.

:ribing the initial temperature rises to maxima in experiment IV to
э added thermal capacity of the thermocouple-supporting Plexiglas rod
l to the low thermal conductivities of yolk and white in near-intact
gs is logical. However, it is also possible that the membranes
)arating the various layers provided a major contribution to the low
ermal conductivities. If this were the case, the fragmentation of
:h membranes in the process of mixing the contents of the egg used in
periment V could have been the major factor responsible for the
sence of such maxima in that experiment.

explained was the observation that the cooling curves for center and
rface of the egg with mixed contents (Fig. 7) were essentially
lncident and lower (by about 1 deg C at 10 min) than the coincident
rves for depths 10 and 20 mm, particularly since all four temperatures
re approximately the same (38 deg C) just after exposure.

spite the uncertainties above, the assessment by the authors of the
udy by Van Ummersen (1961) is valid. They also stated: "Were it not
r the elegant study by Fisher, Lauber, and Voss (1979), we would be
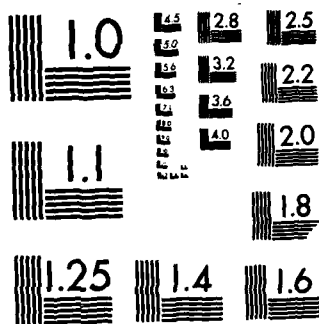
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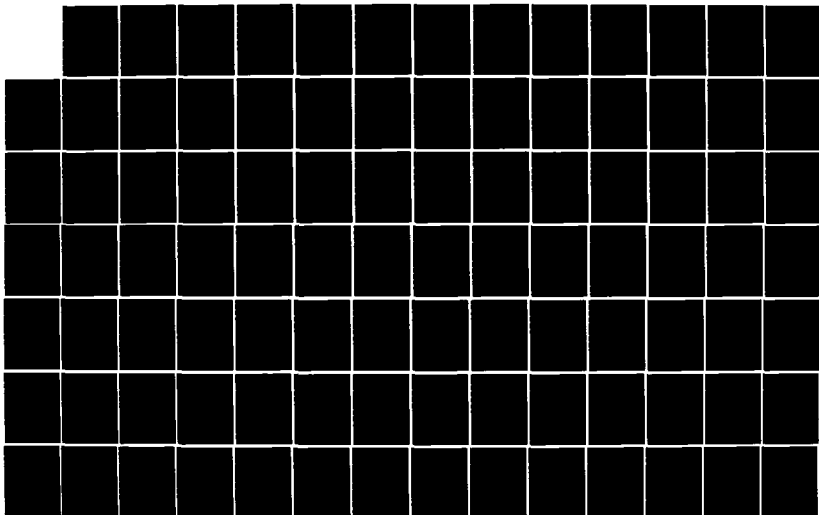
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tempted to attribute Van Ummersen's results solely to thermal effects—albeit specialized thermal effects peculiar to microwave irradiation and not practically reproducible by conventional (conductive or convective) heating. Fisher et al. incubated 4- and 5-day-old chick embryos in a 2.45-GHz field at sub-optimal temperatures (32 to 36 deg C) and found a qualitative synergism between low-level microwave irradiation and ambient temperature, leading to a differential rate of embryonic development. The authors conjecture that two discrete phenomena are involved and that the degree to which either is manifest is somehow temperature dependent." However, the data presented in the paper by Fisher et al. (1979) were also inadequate to support their conclusions.

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Lary, J.M., D.L. Conover, E.D. Foley, and P.L. Hanser
TERATOGENIC EFFECTS OF 27.12 MHZ RADIOFREQUENCY RADIATION IN RATS

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AUTHOR ABSTRACT: High-intensity 27.12 MHz radiofrequency (RF) radiation
was determined to be teratogenic in rats during most of the gestation
period. Eight groups of pregnant rats were exposed to a magnetic field
strength of 55 amps/meter and an electric field strength of 300
volts/meter on gestational days 1, 3, 5, 7, 9, 11, 13, or 15. Exposures
ceased once the dam's colonic temperature reached 43.0 deg C (about
20-40 minutes' duration). Eight matching control groups were sham-
irradiated for 30 minutes at 0 amps/meter and 0 volts/meter. An
additional group of pregnant rats received no treatment.

With one exception, no significant differences occurred between sham-
irradiated and untreated control groups. RF exposure, however, caused a
significant incidence of fetal malformations throughout the post-
implantation period (days 7 through 15). It also caused a low but
significant incidence of preimplantation malformations. Fetal weight
and crown-rump length were reduced in all postimplantation exposure
groups but were not affected by preimplantation exposure. The incidence
of dead or resorbed fetuses was significantly increased in rats
irradiated on days 7 or 9. The effects observed appeared to be caused
by RF-induced hyperthermia in the treated dams. Since a number of
industrial, scientific, and medical devices operating at or near 27.12
MHz can cause hyperthermia in humans, women of childbearing age should
avoid exposure to RF-radiation levels that exceed current US
occupational standards.

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Study Type: Teratology and Developmental Abnormalities, Ocular Effects;
IN VIVO; RAT
Effect Type: RFR-induced embryotoxic and teratogenic effects
Frequency: 27.12 MHz
Modulation: CW
Power Density: 138 mW/sq cm (sum of free-space equivalents of 55 A/m
and 300 V/m)
SAR: 11.1-12.5 W/kg

EXPOSURE CONDITIONS: Eight groups of pregnant rats were exposed to
concurrent CW magnetic and electric fields at 27.12 MHz in a near-field
synthesizer (Greene, 1976) at ambient temperature and relative humidity
maintained at 23 +/- 2 deg C and 45 +/- 10%. Each rat, restrained in a
perforated cylindrical Plexiglas holder, was exposed individually with
its frontal plane perpendicular to the magnetic field and parallel to
the electric field, i.e., if the rat was horizontal and upright, its
long axis was parallel to the (horizontal) magnetic field and
perpendicular to the (vertical) electric field.

One group each (16 to 28 rats) was exposed on gestation day 1, 3, 5, 7, 9, 11, 13, and 15. Colonic temperatures were monitored with a liquid-crystal/fiber-optic probe during exposure. Exposure of each rat was terminated when its colonic temperature reached 43.0 +/- 0.1 deg C (20-40 min). Colonic temperatures were also measured immediately before and after exposure with a thermistor probe. One group each (10 to 13 rats) of eight control groups was sham-exposed for 30 min on the same gestation days. An untreated group (29 rats) maintained in the animal quarters throughout gestation served as cage controls.

OTHER INFORMATION: The exposure conditions were selected to deliver doses that were nearly hyperthermically lethal to the dams. In a pilot study, most of the malformed litters occurred in rats heated by RFR to 43.0 deg C or higher and no malformations were seen at less than 41.9 deg C; colonic temperatures exceeding 43.0 deg C were increasingly lethal, with no rat surviving above 43.5 deg C. In the main study, 26 of the RFR-exposed rats (11%) died from excessive hyperthermia during or shortly after exposure, and only 4 of these had a final temperature of less than 43.0 deg C. None of the sham-exposed or cage-control rats died during the course of the experiment.

The power absorbed by each rat was determined by reflection-coefficient measurements (Greene, 1977), the SAR of the rat (defined as the absorbed power divided by the mass of the rat) was calculated, and the SARs for each group (gestation day) were averaged. The mean SARs ranged from 11.1 to 12.5 W/kg. The mean exposure duration ranged from 26 to 32 min. The colonic temperature at cessation of exposure averaged 43.0 +/- 0.1 deg C, but the individual values ranged from 42.6 to 43.4 deg C because of some instability in the liquid-crystal/fiber-optic probe. The temperatures of the sham-exposed rats rose an average of 0.5 deg C because of holder restraint and the presence of the probe.

All rats were euthanized on gestation day 20 (2 days before parturition) to avoid cannibalization of dead or malformed offspring by the dam. The numbers of implantations, live fetuses, and dead or resorbed conceptuses were determined. Also, the corpora lutea of pregnancy in the cage controls were counted, as were those present during the preimplantation period (gestation days 1, 3, and 5) of the RFR- and sham-exposed groups. Each live fetus was sexed, weighed, measured for crown-rump length, and examined externally for gross malformations. One-third of the live fetuses from each litter were selected randomly, dissected, and examined for visceral abnormalities; the remaining fetuses were cleared and stained for skeletal examination.

The results for the group exposed to RFR on each gestation day of the preimplantation period were compared with the combined results of the three groups sham-exposed on those gestation days; the results for each group exposed to RFR during early organogenesis (day 7, 9, or 11) were compared with the combined results for the groups sham-exposed on those gestation days; the two groups RFR-exposed during late organogenesis (day 13 or 15) were similarly treated. To assess whether the sham-exposed rats were affected significantly by handling, transport, or

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restraint, their results were compared with those of the cage controls.

Litter averages for each parameter were compared by a one-way analysis of variance followed by Dunnett's t-test. For cases where the mean malformation rates of some groups being compared were zero (for which analysis of variance was not appropriate), comparisons were made of the percentage of fetuses affected in each group by use of Fisher's exact test with Bonferroni's correction, after ascertaining that the effect was not confined to only a few litters. The proportions of litters having at least one malformation or resorption were also compared by the latter test.

The results on embryotoxicity indicated that the cage controls and the rats sham-exposed did not differ significantly from one another at each gestation stage. Specifically, the percentages of preimplantation loss and dead or resorbed conceptuses for the rats sham-exposed during the preimplantation period were higher than for the cage controls, but the differences were not statistically significant (p>0.05), and neither were the differences in mean fetal weight and mean crown-rump length between the cage controls and the sham groups at each of the three gestation stages.

The mean fetal crown-rump lengths for the rats exposed to RFR on days 1, 3, and 5 were each slightly lower than for the combined groups of rats sham-exposed during that gestation stage, but only the differences for days 1 and 5 were significant. The percentages of dead or resorbed conceptuses for the rats exposed to RFR on gestation days 7, 9, and 11 were 29%, 49%, and 18%, respectively, as compared with 11% for the combined groups of rats sham-exposed on those days; only the differences of percentages for days 7 and 9 were significant. In addition, the fetal weights and crown-rump lengths for the RFR rats on each of these days were both significantly lower than for the combined sham groups. This was also true for the values of these two parameters on days 13 and 15 relative to the means for the combined sham groups for that gestation stage. Thus, maximum embryotoxicity was induced by exposure to the RFR on gestation day 9.

Regarding the occurrence of terata, the differences in percentages of external, skeletal, or visceral abnormalities between the fetuses of the cage controls and those of the sham-exposed rats were nonsignificant with one exception: 4% of the fetuses of the rats sham-exposed during organogenesis (day 7, 9, or 11) exhibited major visceral abnormalities as compared with 0% of the cage-control fetuses, a significant difference. The percentages of fetal external abnormalities were 0 for all the sham groups, but significant percentages were found for the RFR groups on all days except 1 and 5, with the largest value (67%) for day 9. Significant differences between RFR and sham groups for major skeletal abnormalities were obtained for all days except 3, 5, and 13, with maximum value (60%) again on day 9. Skeletal variations were significant for all days, with day 9 once more yielding the largest value (83%). Major visceral abnormalities were significant only for day 9 (65%). No significant sex-related differences were found.

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Only 3 preimplantation fetuses, 5 early-organogenesis fetuses, and 1 late-organogenesis fetus of the sham groups were abnormal, and only 3 cage-control fetuses were abnormal. In the RFR-exposed groups, more than 200 types of abnormalities were observed, most of which occurred only once. The types of abnormalities observed for each gestation day in two or more fetuses and their incidences were presented in Table 5 of the paper. The greatest variety of abnormalities (17) occurred for exposure on gestation day 9: Microphthalmia or anophthalmia with associated small, narrow cranial orbits were present in 25-39% of all viable fetuses; exencephaly and the associated defects of protruding tongue and aplasia of the upper cranial bones were evident in 17-22% of the fetuses; and other severe malformations were seen in 6-14% of the fetuses.

In their discussion, the authors noted that since most of the general population is exposed to very low environmental levels of RFR, thermal damage to the human embryo from such exposure is most unlikely. However, they pointed out that the levels of occupational exposure can be much higher, and suggested that: "Until the potential for human RF/microwave teratogenesis is determined and safe exposure levels are established, care should be taken to ensure that pregnant women are not exposed to levels that exceed the current U.S. occupational standard."

CRITIQUE: This was a well-designed and executed study, with adequate numbers of RFR- and sham-exposed rats for each gestation day and of cage controls.

Based on their results, the authors noted that the incidence of fetal malformations appears to be related to the degree of hyperthermia induced in the dams by RFR. Since most of the malformations caused by exposure to RFR during the postimplantation period were gestation-day specific, the authors suggested that the majority of abnormalities were due to excessive heating of the fetuses themselves during exposure, citing Edwards (1978), who demonstrated that heat itself can damage the developing embryo and fetus.

On the other hand, the authors did not rule out the possibility of "nonthermal" teratogenic effects of RFR, citing several studies in which teratogenic effects were reported at RFR levels that did not increase maternal core temperatures significantly (Bereznitska and Rysina, 1974; Shore et al., 1977; Berman et al., 1978). However, direct comparisons of their findings with those of the investigators cited would be inappropriate because of the differences in frequencies and animals used and because those investigators exposed their animals daily (mice to 3 GHz at 10 mW/sq cm for 2 hr, mice to 2.45 GHz at 3.4-28 mW/sq cm for 100 min, and rats to 2.45 GHz at 10 mW/sq cm for 5 hr, respectively) for a major part of the gestation period. In this context, Lary et al. (1982) noted that RFR levels insufficient to cause noticeable increases in maternal core temperature could still produce localized uterine heating.

In a more comparable investigation, Berman et al. (1981) exposed pregnant rats to 2.45-GHz RFR at 28 mW/sq cm (4.2 W/kg) for 100 min

daily on gestation days 6 through 15 (similar to the mouse study by Berman et al., 1978). The mean colonic temperature at the end of each exposure was 40.3 deg C. They found no significant teratogenic effects, and remarked that the mouse as a surrogate for humans may be a better model for such studies than the rat. However, neither kind of rodent appears to be a satisfactory model for studying RFR-teratogenesis, because their thermoregulatory systems are both less efficient than the human system. It is interesting that a similar point was made by Bereznitskaya and Rysina (1974). Their concluding sentence was: "A definitive decision as to the danger of radiowaves for the human embryo can come only from a comparison of clinical [human] and experimental [animal] data."

As described in an abstract, Lary et al. (1981) ascertained that the colonic-temperature threshold for embryotoxic and teratogenic effects induced by exposure to 27.12-MHz RFR (at the same level as before) on gestation day 9 for 45 min was 41.5 deg C. Lary et al. (1983) then studied the effects of exposure duration on day 9 at constant colonic temperatures of 42.0 and 41.0 deg C, i.e., just above and below the threshold, and found that the threshold was lowered by protracted exposure.

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Lary, J.M., D.L. Conover, P.H. Johnson, and J.R. Burg
TERATOGENICITY OF 27.12-MHZ RADIATION IN RATS IS RELATED TO DURATION OF
HYPERTHERMIC EXPOSURE

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AUTHOR ABSTRACT: Five groups of pregnant Sprague-Dawley rats were
either sham exposed or were irradiated in a 27.12-MHz radiofrequency
(RF) field at 55 A/m and 300 V/m on gestation day 9. The absorbed power
(approximately 11 W/kg) caused a relatively rapid increase in the rat´s
colonic temperature. Rats in group I were sham irradiated for 2.5 h at
0 A/m, 0 V/m. In group II RF irradiation was terminated after the rat´s
colonic temperature reached 41.0 deg C. In group III the 41.0-deg-C
temperature was maintained an additional 2 h by manually varying the
incident field strength. In group IV irradiation was terminated after
the rat´s colonic temperature reached 42.0 deg C. In group V the 42.0-
deg-C temperature was maintained an additional 15 min by varying the
field strength.

At both temperatures the teratogenic and embryotoxic effects of the RF-
induced hyperthermia increased as the exposure duration increased, but
the increase was especially noticeable at 42.0 deg C. The results
indicate that the teratogenic and embryotoxic effects of RF-induced
hyperthermia are related to both the temperature of the dam during
exposure and the length of time the dam´s temperature remains elevated.

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Study Type: Teratology and Developmental Abnormalities; IN VIVO; RAT
Effect Type: RFR-induced embryotoxic and teratogenic effects
Frequency: 27.12 MHz
Modulation: CW
Power Density: 138 mW/sq cm (sum of free-space equivalents of 55 A/m
and 300 V/m)
SAR: 10.8 W/kg

EXPOSURE CONDITIONS: Pregnant rats were exposed to concurrent CW
magnetic and electric fields at 27.12 MHz in a near-field synthesizer
(Greene, 1976) at ambient temperature and relative humidity maintained
at 24.0 +/- 0.3 deg C and 55 +/- 5%. Each rat, restrained in a
perforated cylindrical Plexiglas holder, was exposed individually witl·
its long axis perpendicular to the magnetic field and parallel to the
electric field. Five groups (each 30 to 41 rats) were treated on
gestation day 9. Colonic temperatures were monitored with a liquid-
crystal/fiber-optic probe during exposure and were also measured
immediately before and after exposure with a thermistor probe.

Group I was sham-exposed for 2.5 hr. Their mean colonic temperature at
the end of the period was 38.1 deg C. The rats in group II were exposed
to the RFR, which was terminated when the colonic temperature reached

41.0 deg C (14-22 min). The rats in group III were similarly treated, but the colonic temperature was maintained at 41.0 +/- 0.1 deg C for an additional 2 hr by manually switching the RFR on and off (total exposure time 137-144 min). Exposure of each rat in group IV was terminated when its temperature reached 42.0 deg C (13-33 min). The rats in group V were similarly treated, but their temperatures were held at 42.0 +/- 0.1 deg C for 15 min more (34-55 min total) by on-off switching.

OTHER INFORMATION: In two previous studies, Lary et al. (1981, 1982) found that the developing rat fetus was maximally affected by 27.12-MHz concurrent magnetic and electric fields (55 A/m and 300 V/m) for acute exposure of the dam on gestation day 9, and that the colonic-temperature threshold for both embryolethality and fetal malformations was about 41.5 deg C. The exposure conditions described above were selected to determine the effect of exposure duration that yielded and maintained colonic temperatures just above and below the teratogenic threshold.

The power absorbed by each rat was determined by reflection-coefficient measurements (Greene, 1977) and the SAR of the rat (defined as the absorbed power divided by the mass of the rat) was calculated. The mean SAR was 10.8 W/kg.

All rats were euthanized on gestation day 20 (2 days before parturition) to avoid cannibalization of dead or malformed offspring by the dam. The numbers of implantations, live fetuses, and dead or resorbed conceptuses were determined. Each live fetus was sexed, weighed, measured for crown-rump length, and examined externally for gross malformations. One-third of the live fetuses from each litter were selected randomly, dissected, and examined for visceral abnormalities; the remaining fetuses were cleared and stained for skeletal examination. All teratological examinations were conducted blind. Comparisons of results were done with a one-tailed t-test on the Freeman-Tukey transformation of percent of abnormalities per litter and percent of dead or resorbed conceptuses per litter, and with a one-sided t-test on nontransformed mean fetal weight and mean crown-rump length.

Approximately two thirds of the rats bred and treated were actually pregnant at euthanasia. There were no apparent differences in mating weight, exposure weight, or colonic temperature just prior to exposure between pregnant and nonpregnant rats or among the different exposure groups. The results on embryotoxicity and teratogenesis were presented respectively in Tables 1 and 2 of the paper.

From Table 1, the mean percentage of dead or resorbed conceptuses per litter (and SE) for group I (sham-exposed; 23 litters) was 10.1 +/- 2.3. The values for groups II (exposure terminated at 41.0 deg C; 21 litters) and III (2 additional hr at 41.0 deg C; 22 litters) were 9.6 +/- 2.1 and 9.2 +/- 3.1, respectively. The differences among the three means were nonsignificant (p>0.05). Thus, exposure to attain 41.0 deg C or prolongation of that temperature for 2 hr had no significant effect on this endpoint. The values for groups IV (exposure terminated at 42.0 deg C; 23 litters) and V (15 additional min at 42.0 deg C; 24 litters)

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were 14.7 +/- 3.5 and 22.5 +/- 4.9. The difference between these two means was significant (p<0.05) but none of the other differences was significant. Thus, embryotoxicity was nonsignificantly increased by exposure to attain 42.0 deg C, and prolongation of exposure at that temperature for 15 min yielded a significant increase.

The mean fetal weights per litter (in grams) for groups I-V were 3.61 +/- 0.09, 3.65 +/- 0.05, 3.47 +/- 0.06, 3.43 +/- 0.08, and 3.39 +/- 0.06, respectively. The corresponding mean fetal crown-rump lengths (in mm) were 37.2 +/- 0.4, 37.4 +/- 0.2, 36.6 +/- 0.2, 36.5 +/- 0.3, and 36.1 +/- 0.3. Apparently neither endpoint was affected significantly by exposure to attain 41.0 deg C, but prolongation of that temperature yielded significant decreases of both. However, neither exposure to attain 42.0 deg C nor its prolongation yielded additional significant decreases.

From Table 2 of the paper, the percentages of live fetuses with external malformations for groups I-V (with the ratio of litters affected shown in parentheses) respectively were 0.3 +/- 0.3 (1/23), 1.5 +/- 0.7 (4/21), 2.0 +/- 0.7 (6/22), 4.5 +/- 1.5 (8/23), and 53.2 +/- 7.4 (19/24). Thus, there were monotonic increases in severity in both percentage of malformed fetuses and ratio of litters affected, with by far the largest change for prolongation of 42.0 deg C.

The percentages of live fetuses with visceral malformations were 1.9 +/- 1.3 (2/21), 0 (0/20), 2.0 +/- 1.4 (2/22), 4.1 +/- 1.9 (4/23), and 53.4 +/- 7.5 (17/21). The 0% for group II may have been a statistical anomaly, since the means and SEs for groups I and III were almost the same. Again, the largest change occurred for prolonged exposure at 42.0 deg C.

The percentages of live fetuses with major skeletal abnormalities were 1.4 +/- 0.9 (2/23), 1.5 +/- 0.8 (3/21), 6.0 +/- 2.0 (8/22), 8.4 +/- 2.5 (10/23), and 49.3 +/- 7.3 (19/24). The difference in means for exposure to attain 41.0 deg C and prolonging that temperature was significant, as was the corresponding difference for 42.0 deg C.

The percentages of live fetuses with minor skeletal variations were 30.4 +/- 5.7 (18/23), 30.1 +/- 4.9 (18/21), 54.5 +/- 6.0 (22/22), 60.1 +/- 6.5 (23/23), and 72.0 +/- 6.8 (22/24), with only the difference for 41.0 deg C and its prolongation significant.

CRITIQUE: From Lary et al. (1982): "Each rat was oriented so that its frontal plane was perpendicular to the incident magnetic field and parallel to the incident electric field." Based on this statement, the rat's long axis was parallel to the magnetic field and perpendicular to the electric field, which was a different orientation than that used in the present investigation (see EXPOSURE CONDITIONS above). The authors did not mention this change or any reason for selecting either orientation in preference to others, leading the reviewer to speculate that perhaps no change was made and that one of the descriptions was in error. Possibly related to this point is that the mean SAR in the

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:esent study (10.8 W/kg) was lower than the range of means in the
revious study (11.1-12.5 W/kg) even though the amplitudes of the fields
are the same, but differences in dam weight might have been the primary
actor. However, these points may not have much biological significance
ecause the exposure endpoints sought were predetermined colonic
emperatures rather than SARs.

s in Lary et al. (1982), the authors ascribed the observed teratogenic
ffects to the hyperthermia induced by the RFR, citing the study by
dwards (1978), who demonstrated that excessive heat per se is a
eratogen. In the present study, they also developed experimental
vidence that the colonic-temperature threshold for teratogenesis (41.5
leg C; Lary et al., 1981) is lower for prolonged hyperthermic exposure.

is noted by Lary et al. (present study), the existence of a colonic-
:emperature threshold for teratogenesis in the rat is supported by the
in-vitro results of Cockcroft and New (1975), who subjected explanted
cat embryos grown in culture during gestation days 10-12 to incubation
at a temperature of 40 or 41 deg C (2-3 deg C above normal) for 12-46
hr. Nearly all of the embryos incubated at 41 deg C developed severe
abnormalities, as compared with only about half of those incubated at 40
deg C.

The results of Berman et al. (1981) are also pertinent. They exposed
pregnant rats to 2.45-GHz RFR at 28 mW/sq cm (4.2 W/kg) for 100 min
daily on gestation days 6 through 15. The mean colonic temperature at
the end of each exposure was 40.3 deg C. They found no significant
teratogenic effects. On the other hand, Berman et al. (1978) also
exposed mice to 2.45-GHz RFR at SARs of 2.0 to 22.0 W/kg for 100 min per
day on gestation days 1 through 17, which yielded colonic-temperature
increases of less than 1 deg C. They reported significantly lower mean
live fetal weight per litter and significantly higher incidence of
cranioschisis at 22 W/kg, and remarked that the mouse as a surrogate for
humans may be a better model for such studies than the rat. However,
neither kind of rodent appears to be a satisfactory model for studying
RFR-teratogenesis, because their thermoregulatory systems are both less
efficient than the human system.

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but the males were unaffected. Irradiated females exhibited decreased
activity levels, and males showed increased activity levels, in the open
field test. (Note by reviewer: The last two statements appear to be
contrary to the behavioral results discussed above.) Subtle shifts in
the Fla population reproductive parameters indicate possible long-term
irradiation effects. These studies indicate that this power density
level at this frequency may be deleterious to the rat, but that lower
power density levels may not be. Functional evaluations are not
conclusive in the absence of correlative structural data, since
functional data are an addition to and not a substitute for structural
data." (Note by reviewer: The statements regarding decreased female
learning ability and activity appear to be contrary to the results
reported in the body of the paper.)

CRITIQUE: This study, its companion one (Jensh, 1984a), and two
previous pairs of studies (Jensh et al., 1982a, 1982b at 915 MHz; Jensh
et al., 1983a, 1983b at 2.45 GHz) collectively comprise a remarkable,
comprehensive investigation of possible RFR-induced teratogenesis and
developmental abnormalities in the rat. Especially noteworthy in the
present study are the large quantities of data collected over several
generations.

As in the earlier studies, two different groups of baseline controls (HC
and AC) were used, as well as a sham-exposed group, with a view toward
assessing whether non-RFR factors were present. (Once again, however,
the distinction in treatment between the AC and sham groups was not
clear.) The occurrence of statistically-significant differences between
the sham and the two baseline groups and between the latter groups
suggests that such factors may have been present, rendering it difficult
to ascertain the extent to which the reported differences between the
RFR and sham groups were due to RFR exposure. For example, even though
the mean weight RFR-exposed Fla pups at age 3 days was significantly
smaller than for the concurrently sham-exposed pups, it would be
questionable to regard the RFR-exposed pups as underdeveloped, since the
mean weight of the AC group was and remained significantly lower than of
the RFR group. Also, the occurrence of significant behavioral
differences between females and males is an interesting finding, but
difficult to ascribe to RFR exposure per se.

A noteworthy point regarding the use of multiple behavioral tests on the
same rats is an investigation (not involving RFR) by Jensh et al. (1981)
showing that performance of a task by rat offspring does not alter
significantly the subsequent performance of an unrelated task.

Perhaps the most important finding of this study was the absence of any
terata in Fla, Flb, and F2 offspring from prolonged exposure of rats (8
hr/day throughout their first pregnancy) to 6-GHz RFR at 35 mW/sq cm
(whole-body SAR of about 7 W/kg). (The few cataracts observed in the
Fla offspring appeared to be unrelated to RFR exposure.) This finding
is consonant with the results of Berman et al. (1981) on pregnant rats
exposed to 2.45-GHz RFR for 100 min daily at 28 mW/sq cm (whole-body SAR
of 4.2 W/kg) on gestation days 6 through 15.

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smallest litter size (12.2) occurred in the irradiated female x irradiated male group, the two irradiated x colony control groups were intermediate, and the sham female x sham male group was the lowest in resorption rate (4.5%) and largest in litter size (14.8). Correlation coefficient analyses revealed a significant direct correlation between maternal weight gain and mean litter size (P<0.05) in all groups." However, t-tests of the data in Table XIV by the reviewer yielded nonsignificant (p>0.05) differences among the four groups in mean F2 litter size and mean fetal weight.

Mean organ-to-body weight ratios of RFR- and sham-exposed adult Fla males (Table XV) differed significantly (p<0.05) only for the left kidney and the right testis, with the mean values larger for the RFR group. However, the values for both groups were significantly larger (p<0.01) than for the baseline HC and AC groups. For the RFR- and sham-exposed females (Table XVI), the only significant ratio difference was for the liver (p<0.02), but again the values for both groups were significantly larger (p<0.001) than for the HC and AC groups.

The author summarized the results for hematocrit, hemoglobin, and white blood cell counts (presented in Tables XVII and XVIII) as follows:

"Nonpregnant females and pregnant term females also did not differ significantly (P>0.05) among all groups across the two generations. In every instance, when pregnant term females were compared with nonpregnant females, males from either of the two concurrent control groups (sham or colony control), and across two generations, there was a statistically significant difference (P<0.05), the pregnant females having markedly lower hematocrit values."

"Comparison of hemoglobin values indicated that these blood levels were significantly decreased in all pregnant females in all groups across two generations when compared to males (P<0.001) and all nonpregnant females (P<0.05) except the colony control rebred nonpregnant females."

"Statistical analysis of white blood cell counts indicated that Fla irradiated males had a significantly higher (P<0.05) count compared to concurrent control males or to irradiated or control females (pregnant or nonpregnant) across two generations. Statistical analysis of the differential white blood cell counts (Table XVIII) indicated that pregnant females had a significantly higher neutrophil count and a correspondingly lower lymphocyte count than nonpregnant females (P<0.05). Nonpregnant females had an average neutrophil count of 15 and an average lymphocyte count of 78. Neutrophil and lymphocyte counts of males were intermediate."

In his overall summary and conclusion, the author stated: "Several subtle psychophysiologic alterations occurred in animals exposed in utero to a 35 mW/sq cm power density level of 6000-MHz microwave radiation in the absence of morphologic alterations. The sexes appeared differentially affected by exposure to this radiation. Irradiated females exhibited decreased learning ability in the water T maze test

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week later were similar. However, the author noted that the RFR-exposed females consistently made more premature crossings than the sham-exposed females. Table XI also showed no significant differences in mean numbers of shock avoidances on test and retest among the combined male and female RFR, sham, and baseline groups, but the author noted that the sham-exposed females had significantly more shock avoidances and fewer shocks than the sham-exposed males.

Table VIII showed that there were no significant differences in mean time for the water T maze between the males and females of either group or between the RFR and sham groups of either sex. However, 77% of the RFR-exposed females achieved criterion performance, compared with 100% for the sham-exposed females. The corresponding values for the males were 93% and 94%, yielding totals of 84% for the RFR-exposed rats and 96% for the sham-exposed rats.

Regarding the swimming tests, the author stated: "Statistical analyses invariably indicated that when significant differences (P<0.05) occurred between the baseline control and the irradiated groups, significant differences also occurred between the baseline and concurrent control [sham-exposed] groups."

The results of the open-field, hanging, and activity-wheel tests, presented in Table XIII without regard to sex, showed no significant differences between RFR- and sham-exposed rats, but both groups differed significantly from the baseline controls in hanging and activity.

The results of breeding the adult Fla rats (Table XIV) were that the mean maternal weight increase during gestation of (in-utero) RFR-exposed females bred with RFR-exposed males (32.7%) was significantly less than for colony-control females bred with RFR-exposed males (44.7%) or for RFR-exposed females bred with colony-control males (37.0%) or for sham-exposed females bred with sham-exposed males (39.5%). Also significant was the weight-increase difference between the colony-control females mated with RFR-exposed males (44.7%) and RFR-exposed females mated with colony-control males (37.0%).

Table XIV showed no data on breeding of colony-control rats with colony-control rats or with sham-exposed rats of either sex; however, the author stated: "The group in which only the mother was irradiated (irradiated female x colony control male) did not significantly differ (P>0.05) in weight gain from the colony control female x sham male group but did differ significantly (P<0.05) from the colony control female x irradiated male group as well as the sham female x sham male group (P<0.01)." (Reviewer note: by t-test, the last difference, 37.0% vs 39.5%, was not significant.)

Regarding the resulting (F2) offspring, the author stated: "Mean litter sizes differed significantly only between the irradiated female x irradiated male and the sham female x sham male groups (P<0.05). Both the litter size and the resorption rate varied inversely with the exposure groups. That is, the highest resorption rate (8.7%) and the

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were performed; and the ovaries or testes, livers, kidneys, and brains were removed, weighed, fixed, and given histopathologic analysis. At ages 90–120 days, the other male and female Fla offspring were bred in various combinations of RFR, sham, and baseline HC and AC mates to assess reproductive ability. The bred male and female Fla rats were given organ and blood analyses and the resulting F2 term fetuses were assessed for teratogenic effects.

From Table II of the paper, the mean maternal weights and SDs for 9 sham and 11 RFR dams on gestation day 0 of the first breeding were 222.4 +/- 35.4 and 202.6 +/- 19.0 g, respectively. By t-test, the difference was nonsignificant (p>0.05). The values for the sham and RFR dams on gestation day 21 were 402.6 +/- 49.8 and 349.9 +/- 31.7 g, a significant difference (p<0.02). These values represented mean weight gains of 45.2% for the sham dams and 42.1% for the RFR dams. The mean litter size for the RFR dams was 9.55 +/- 4.32 fetuses, as compared with 12.00 +/- 2.92 for the sham group. Table II also showed that although the mean weight gain of the baseline HC group was 45.8%, i.e., close to that of the sham group, the value for the baseline AC group was 42.8% or close to that of the RFR group. The respective mean litter sizes were 12.40 and 11.20.

Examination of the Fla pups on postnatal day 3 (Table III) revealed that 3 pups from 1 of the RFR-exposed dams had cataracts (2 unilateral and 1 bilateral), 1 pup from a sham-exposed dam had bilateral cataracts, and 1 pup from a baseline-AC dam had a unilateral cataract. No other abnormalities were evident.

From Table VII, the mean weights of 63 sham-exposed pups and 68 RFR-exposed pups on day 3 were 9.9 +/- 1.8 and 9.1 +/- 1.1 g, respectively, a significant difference (p<0.01). In subsequent weekly weighings, the differences were progressively less significant, becoming nonsignificant (p>0.05) at about 38 days of age. On day 3, however, the mean weight of 111 baseline-AC pups was only 8.1 +/- 1.6 g and remained significantly lower than for the RFR-exposed pups throughout the subsequent weekly weighings (to age 87 days).

In the reflex and physiologic tests on 55 sham-exposed and 69 RFR-exposed Fla offspring (Table VI), the mean ages for eye opening were 17.4 +/- 1.5 and 16.8 +/- 0.8 days, respectively, a significant difference. (Comparative data were not presented for HC or AC offspring.) Although not mentioned in the text by the author, the mean ages for visual placement shown in Table VI were 24.7 +/- 1.4 and 23.0 +/- 2.2 days, respectively, also a significant difference.

The results for the adult behavioral tests were characterized by large variances for all groups. In the conditioned avoidance response test, the results of which were presented in Table XI without regard to sex, the mean numbers of premature crossings on the 5th day of testing by 29 sham-exposed and 33 RFR-exposed rats were 5.0 +/- 6.1 and 5.5 +/- 7.4, a nonsignificant difference, but both values were significantly lower than for 48 baseline-control rats (21.0 +/- 19.4). The results on retest one

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of up to 4 rats each. Six of the minigroups comprised the RFR group. The rats of each minigroup were exposed concurrently at 35 mW/sq cm throughout the 21-day gestation period for 8 hr/day without food and water. For exposure, each rat was confined unrestrained within an individual Plexiglas cage, which was placed at 1 of the 4 locations of equal power density below the horn. The positions of the cages were varied daily. The other 5 minigroups, comprising the sham group, were sham-exposed concurrently with the RFR group but otherwise treated similarly.

OTHER INFORMATION: Preliminary dosimetry studies were done with male rats of comparable weight. They were exposed at 47, 40, 37, or 35 mW/sq cm for 5 hr. Temperatures were recorded with a rectal thermocouple probe at 15-min intervals for 1 hr before and 1 hr after exposure and at 30-min intervals during exposure. No increase in rectal temperature was observed during 5 hr of exposure at 35 mW/sq cm (data not presented), which led to the use of this level for the dams. The authors stated: "The average SAR was calculated to be 7.28 W/kg using the method of Durney et al. (1978). Average body weight was calculated on the basis of mean initial maternal weight (Day 0 of gestation) and daily weight gains throughout pregnancy."

Comparisons of biological endpoints were made not only between the RFR and sham groups, but also with two groups of baseline controls, one held in home cages for 21 days (HC group), and the other isolated within the anechoic chamber for 21 days (AC group). Both baseline groups were deprived of food and water for 8 hr/day.

On gestation day 22, half the dams of each group were decapitated and studied for teratogenesis, the results of which were presented in a companion paper (Jensh, 1984a). The remaining dams delivered at term (Fla offspring) and the litter size was culled to 4 males and 4 females on postnatal day 1. The Fla offspring were weaned at age 30 days. Ten days after weaning, the dams were rebred for up to 30 days to obtain pregnancy. The pregnant rats were killed on gestation day 22 and the Flb litters were studied for teratogenesis. The nonpregnant rats were killed on day 30; their ovaries, livers, kidneys, and brains were removed, weighed, fixed; and the rats were given organ and blood analyses.

The Fla offspring were examined for gross abnormalities and weighed individually on postnatal day 3, and were subsequently weighed weekly. The following neonatal/perinatal reflex and physiologic tests were initiated for the Fla offspring on the postnatal days indicated in parentheses: surface righting (3), negative geotaxis (7), auditory startle (12), eye opening (12), air righting (15), and visual placing (19). During ages 60-90 days, half the Fla weanlings were also given a conditioned avoidance response test and the other half a water T maze test, after which the rats of both groups each randomly received two of the following tests: open field, activity wheel, swimming, hanging.

Half the Fla offspring were killed at about age 100 days; blood tests

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STUDIES OF THE TERATOGENIC POTENTIAL OF EXPOSURE OF RATS TO 6000-MHZ
MICROWAVE RADIATION—II. POSTNATAL PSYCHOPHYSIOLOGIC EVALUATIONS
Radiat. Res., Vol. 97, No. 2, pp. 282-301 (1984b)

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AUTHOR ABSTRACT: Wistar rats (36) were exposed daily throughout
pregnancy to a power density level of 35 mW/sq cm of 6000-MHz microwave
radiation (11), sham irradiated (10), or used as control animals (15).
Litters were culled to a maximum of eight Fla offspring/litter (total =
124) on Postnatal Day 1 and subjected to a series of reflex tests
beginning Day 3. Mothers were rebred 10 days after weaning.

Teratologic evaluations were completed on 263 Flb offspring. Weekly
weights were recorded for 298 Fla offspring. At 60 days, behavioral
testing was initiated on 121 offspring. At 90 days, offspring were bred
within/across groups. Teratologic evaluations were completed on 659 F2
term fetuses. Organ weight analyses were completed on 17 mothers and
181 Fla adult offspring, and blood analyses on 21 mothers and 131
offspring.

Sex differences within groups were observed in four behavioral tests and
in blood data. Significant differences between groups were observed
for: Flb term fetal weight; Fla eye opening, postnatal growth to the
fifth week, water T-maze and open field test results; and several
organ/body weight ratios. These results indicate that exposure to 6000-
MHz radiation at this power density level may result in subtle long-term
neurophysiologic alterations not detectable at term using conventional
morphologic teratologic procedures.

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Study Type: Teratology and Developmental Abnormalities, Immunology and
Hematology, Ocular Effects; IN VIVO; RAT
Effect Type: Effects of RFR exposure of dams on postnatal development,
behavior, and blood parameters of two generations of offspring
Frequency: 6 GHz
Modulation: CW
Power Density: 35 mW/sq cm
SAR: 7.28 W/kg

EXPOSURE CONDITIONS: Exposures to far-field RFR were done from above
with a standard-gain horn within an air-conditioned anechoic chamber
(temperature not stated; relative humidity and air velocity not
measured). The beamwidth of the horn permitted simultaneous exposure of
rats to the same power density at 4 locations without significant
interanimal field perturbations, and inclusion of a power-density meter
(Narda Radiation Monitor Model 8306B with 8323 probe) at a 5th location.

Forty-two pregnant Wistar rats were randomly assigned to 11 minigroups

Jensh, R.P., W.H. Vogel, and R.L. Brent
AN EVALUATION OF THE TERATOGENIC POTENTIAL OF PROTRACTED EXPOSURE OF
PREGNANT RATS TO 2450-MHZ MICROWAVE RADIATION: II. POSTNATAL
PSYCHOPHYSIOLOGIC ANALYSIS
J. Toxicol. Environ. Health, Vol. 11, No. 1, pp. 37-59 (1983b)

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POSTNATAL FUNCTIONAL ANALYSIS OF PRENATAL EXPOSURE OF RATS TO 915 MHZ
MICROWAVE RADIATION
J. Am. Coll. Toxicol., Vol. 1, No. 3, pp. 73-90 (1982b)

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TERATOLOGIC STUDIES OF PRENATAL EXPOSURE OF RATS TO 915-MHZ MICROWAVE
RADIATION
Radiat. Res., Vol. 92, pp. 160-171 (1982a)

Jensh, R.P., I. Weinberg, and R.L. Brent
AN EVALUATION OF THE TERATOGENIC POTENTIAL OF PROTRACTED EXPOSURE OF
PREGNANT RATS TO 2450-MHZ MICROWAVE RADIATION: I. MORPHOLOGIC ANALYSIS
AT TERM
J. Toxicol. Environ. Health, Vol. 11, No. 1, pp. 23-35 (1983a)

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JENSH

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CW
DEVELOPMENT
EMBRYO
HEMATOLOGY
IMMUNOLOGY
IN-VIVO
LEUKOCYTE
LYMPHOCYTE
RAT
RECTAL
RFR
TERATOGENIC
WEIGHT

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orientations were observed with closed-circuit TV, as noted by the author. Not clear, however, are the statement, quoted above, regarding calculation of the mean SAR (7.28 W/kg), in view of the substantial maternal weight increases during gestation, and the rationale for citing the value to three significant figures. Another obscure point is the use of data on 8-day fetuses in calculating resorption rates, since no mention was made in the paper regarding collection of such data.

The only statistically significant results reported in the present study were the differences between the RFR and sham groups in mean fetal term weight and the maternal monocyte counts. (With regard to the latter finding, the exclusion of the blood-analysis data for 3 of the RFR dams was not explained.) From the foregoing discussion, however, these differences may not have been RFR-related. In view of such uncertainties, perhaps the other points raised above are moot.

Another point of conjecture is whether teratogenic effects would be expected for exposure from above to 6-GHz RFR at 35 mW/sq cm. At this frequency, the penetration depth for muscle is about 0.7 cm, compared with about 2.4 cm at 915 MHz and 1.7 cm at 2.45 GHz. Therefore, the local SARs in the uteri would be much lower at 6 GHz even though the whole-body SAR at that frequency was much larger than in the earlier studies. Support for this point was the absence of rectal-temperature rises in rats after 5 hr of exposure at 35 mW/sq cm. In this context, perhaps it would be misleading to compare whole-body SARs for the three frequencies, and the author did not do so.

Berman et al. (1981) used 2.45-GHz RFR to expose pregnant rats for 100 min daily at 28 mW/sq cm (whole-body SAR 4.2 W/kg) on gestation days 6 through 15. The mean colonic temperature at the end of each exposure was 40.3 deg C. They found no significant teratogenic effects. The negative results of Jensh et al. (1983a, 1983b) at 2.45 GHz support those findings.

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Radiat. Res., Vol. 97, No. 2, pp. 282-301 (1984b)

there were significant differences between the sham and AC groups in the ratios for the brain, liver, and kidneys, but not for the ovaries.

The blood analyses, presented for 7 of the RFR dams and the 8 sham dams, showed no significant differences in hematocrit, hemoglobin, or white blood cell count. Also, the differential white blood cell counts showed no significant differences in neutrophils, eosinophils, or basophils. However, the mean monocyte counts (per 100 leukocytes) were 3.3 +/- 1.7 and 7.4 +/- 4.2, respectively for the RFR and sham dams, and their mean lymphocyte counts were 69.5 +/- 9.3 and 61.4 +/- 5.5. With the 2-tailed t-test, the monocyte-count difference was significant ($p<0.05$) and the lymphocyte-count difference was almost significant. (No blood-analysis data were presented for the HC or AC groups or for 3 of the RFR dams.)

The mean number of fetuses/litter for the 5 HC dams, 10 AC dams, 8 sham dams, and 10 RFR dams ranged from 11.40 to 11.70, with no significant differences among the groups. However, the mean fetal weights (and SDs) were 5.581 +/- 0.349, 5.369 +/- 0.349, 5.902 +/- 0.618, and 5.094 +/- 0.596, respectively. The difference in values between the RFR and sham groups was highly significant ($p<0.001$), but so was the difference between the sham and AC groups and between the HC and AC groups. There were no significant differences in resorption rate, defined as the total number of resorptions divided by the total number of 8-day fetuses.

Of 57 term fetuses from the HC dams and 93 fetuses from the AC dams, none was abnormal. One of 117 fetuses from the sham dams was born dead, was macerated, and had multiple malformations, and one of 117 fetuses from the RFR dams had a curly tail.

CRITIQUE: This study and its companion one (Jensh, 1984b) were similar to two earlier pairs of studies, all of which were well designed and conducted. In Jensh et al. (1982a, 1982b), pregnant Wistar rats were exposed throughout gestation to 915-MHz RFR at 10 mW/sq cm (3.57 W/kg) instead of 6-GHz RFR at 35 mW/sq cm (7.28 W/kg). In Jensh (1983a, 1983b), pregnant Wistar rats were similarly exposed to 2.45-GHz RFR at 20 mW/sq cm (4.38 W/kg). No significant teratogenic effects were observed in either pair of earlier studies.

Especially noteworthy was the use of two different groups of baseline controls (HC and AC) as well as a sham-exposed group, with a view toward assessing whether non-RFR factors were present. (However, as in the earlier studies, the distinction in treatment between the AC and sham groups is not clear.) Statistically-significant differences in some results between the sham and the two baseline groups and between the latter groups were found, which does suggest that such factors may have been present. Thus, at best, the only basis for comparison for RFR-induced effects would be between the RFR and sham groups.

In Jensh et al. (1982a, 1982b), the antenna was rotated at 30 rpm during exposure, to avoid rat selection of preferential orientations relative to the field vectors. Use of this measure was not mentioned in the present paper; presumably it was not used, because no preferential rat

Forty-two pregnant Wistar rats were randomly assigned to 11 minigroups of up to 4 rats each. Each of 6 minigroups, comprising the RFR group, was exposed at 35 mW/sq cm throughout the 21-day gestation period for 8 hr/day without food and water. For exposure, each rat was confined unrestrained within an individual Plexiglas cage, which was placed at 1 of the 4 locations of equal power density below the horn. The positions of the cages were varied daily. The other 5 minigroups, comprising the sham group, were sham-exposed concurrently with the RFR group but otherwise treated similarly.

OTHER INFORMATION: Preliminary dosimetry studies were done with male rats of comparable weight. They were exposed at 47, 40, 37, or 35 mW/sq cm for 5 hr. Temperatures were recorded with a rectal thermocouple probe at 15-min intervals for 1 hr before and 1 hr after exposure and at 30-min intervals during exposure. No increase in rectal temperature was observed during 5 hr of exposure at 35 mW/sq cm (data not presented), which led to the use of this level for the dams. The authors stated: "The average SAR was calculated to be 7.28 W/kg using the method of Durney et al. (1978). Average body weight was calculated on the basis of mean initial maternal weight (Day 0 of gestation) and daily weight gains throughout pregnancy."

Comparisons of biological endpoints were made not only between the RFR and sham groups, but also with two groups of baseline controls, one held in home cages for 21 days (HC group), and the other isolated within the anechoic chamber for 21 days (AC group). Both baseline groups were deprived of food and water for 8 hr/day and were euthanized on day 21.

On gestation day 22, half the dams of each group were decapitated. The remaining dams were used for postnatal analysis, as discussed in a companion paper (Jensh, 1984b). Two of the sham dams and 1 RFR dam were found to be not pregnant, leaving 8 pregnant sham dams and 10 RFR dams. For comparisons, the HC and AC groups consisted of 5 and 10 pregnant dams, respectively. The numbers of implantation sites and dead and live fetuses, and their positions within the uteri were recorded. Maternal brain, liver, kidneys, and ovaries were removed, weighed, and fixed. Blood samples taken from the dams were analyzed for hematocrit, hemoglobin, white blood cell count, and white blood cell differential count. Each fetus and its placenta, excluding membranes, was weighed and examined for gross abnormalities. The fetuses were then fixed, stored, dissected, and examined for abnormalities.

The difference in mean maternal weight on gestation day 0 between the RFR and sham groups was nonsignificant (p>0.05), which was also true for the difference between the HC and AC groups, but the values for the former groups were larger than for the latter groups, with the difference between the sham and AC groups significant (p<0.05). On gestation day 21, none of the differences in maternal weight among the groups was significant. There were also no significant differences between the RFR and sham groups in maternal organ weights or organ-to-body-weight ratios for the brain, liver, kidneys, or ovaries, which was also true for the differences between the HC and AC groups. However,

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Jensh, R.P.
STUDIES OF THE TERATOGENIC POTENTIAL OF EXPOSURE OF RATS TO 6000-MHZ
MICROWAVE RADIATION--I. MORPHOLOGIC ANALYSIS AT TERM
Radiat. Res., Vol. 97, No. 2, pp. 272-281 (1984a)

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AUTHOR ABSTRACT: Thirty-six pregnant Wistar strain albino rats were
exposed throughout pregnancy to 6000-MHz microwave radiation at a power
density level of 35 mW/sq cm or were used as controls. The irradiation
did not cause a significant increase in maternal body temperature as
measured by a rectal thermocouple. The rats were assigned to one of
four groups: home cage control (5), anechoic chamber control (10), sham-
irradiated concurrent control (10), and irradiated (11).

All animals were killed on the 22nd day of gestation, and maternal
tissues were removed and weighed and maternal blood samples were taken.
The 384 resultant fetuses and their placentas were individually weighed,
fixed, and dissected to determine normality. Teratologic evaluation
included the following parameters: maternal weight and weight gain; mean
litter size; maternal organ weight and organ weight/body weight ratios;
body weight ratios of brain, liver, kidneys, and ovaries; maternal
peripheral blood parameters including hematocrit, hemoglobin, and white
cell counts; number of resorptions and resorption rate; number of
abnormalities and abnormality rate; mean term fetal weight.

The irradiated fetuses exhibited slight but statistically significant
growth retardation at term. Term maternal monocyte count was also
significantly depressed. No other parameters differed between the
control groups and the irradiated group.

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Study Type: Teratology and Developmental Abnormalities, Immunology and
Hematology; IN VIVO; RAT
Effect Type: RFR-induced alterations of maternal weight and organ
weight, maternal peripheral blood parameters, and effects on conceptus
resorption rate, fetal abnormalities, and mean fetal term weight
Frequency: 6 GHz
Modulation: CW
Power Density: 35 mW/sq cm
SAR: 7.28 W/kg

EXPOSURE CONDITIONS: Exposures to far-field RFR were done from above
with a standard-gain horn within an air-conditioned anechoic chamber
(temperature not stated; relative humidity and air velocity not
measured). The beamwidth of the horn permitted simultaneous exposure of
rats to the same power density at 4 locations without significant
interanimal field perturbations, and inclusion of a power-density meter
(Narda Radiation Monitor Model 8306B with 8323 probe) at a 5th location.

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DEVELOPMENT
EMBRYO
EXPOSURE-SYSTEM
HYPERTHERMIA
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Teratology, Vol. 26, No. 3, pp. 299-309 (1982)

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JENSH

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BEHAVIOR
CW
DEVELOPMENT
EMBRYO
HEMATOLOGY
IMMUNOLOGY
IN-VIVO
LEUKOCYTE
LYMPHOCYTE
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de Lorge, J.O.
OPERANT BEHAVIOR AND COLONIC TEMPERATURE OF MACACA MULATTA EXPOSED TO
RADIO FREQUENCY FIELDS AT AND ABOVE RESONANT FREQUENCIES
Bioelectromagnetics, Vol. 5, No. 2, pp. 233-246 (1984)

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AUTHOR ABSTRACT: Five food-deprived rhesus monkeys were exposed to
225-MHz continuous-wave, and 1.3-GHz, and 5.8-GHz pulsed radiation to
determine the minimal power densities affecting performance. The
monkeys were trained to press a lever (observing-response) thereby
producing signals that indicated availability of food. In the presence
of the aperiodically appearing food signals, a detection response on a
different lever was reinforced by a food pellet. Continuous, stable
responding during 60-min sessions developed and was followed by repeated
exposures to radiofrequency radiation. The subjects, restrained in a
Styrofoam chair, were exposed to free-field radiation while performing
the task. Colonic temperature was simultaneously obtained.

Observing-response performance was impaired at increasingly higher power
densities as frequency increased from the near-resonance 225 MHz to the
above-resonance 5.8 GHz. The threshold power density of disrupted
response rate at 225 MHz was 8.1 mW/sq cm; at 1.3 GHz it was 57 mW/sq
cm, and at 5.8 GHz it was 140 mW/sq cm. These power densities were
associated with reliable increases in colonic temperatures above
sham-exposure levels. The mean increase was typically in the range of 1
deg C, and response-rate changes were not observed in the absence of
concomitant temperature increases. In these experiments increase of
colonic temperature was a much better predictor of behavioral disruption
than was either the power density of the incident field or estimates of
whole-body-averaged rates of energy absorption.

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Study Type: Behavior, Physiology and Biochemistry, Metabolism and
Thermoregulation; IN VIVO; RHESUS MONKEY
Effect Type: Thresholds for operant-behavioral disruption from exposure
to RFR at frequencies near and above resonance
Frequency: 0.225, 1.3, or 5.8 GHz
Modulation: CW at 225 MHz; 3-microsecond 1.3-GHz pulses at 370 pps
(0.0011 duty); 0.5- or 2-microsecond 5.8-GHz pulses at 662 pps (0.00033
or 0.0013 duty)
Power Density: 5-11 mW/sq cm Av (CW) at 225 MHz, 20-95 mW/sq cm Av at
1.3 GHz, and 11-150 mW/sq cm Av at 5.8 GHz at the center of the monkey's
head in the absence of the monkey and its restraining chair
SAR: 2.0-4.4 W/kg at 225 MHz, 2.6-12.4 W/kg at 1.3 GHz, 0.34-4.7 W/kg
at 5.8 GHz

EXPOSURE CONDITIONS: Each of 5 male monkeys seated in a Styrofoam
restraining chair was exposed frontally, during 1-hr sessions, to
vertically polarized RFR at one of the three frequencies from a horn in

a ventilated anechoic chamber designed for that frequency. Exposures to 225 GHz were with the center of the monkey's head at 0.78 of the conventional far-field distance from the horn. The distances were varied for the other two frequencies, but were never less than 0.57 and 0.53 of the far-field distances for 1.3 and 5.8 GHz, respectively. Within each chamber was a 25-W incandescent lamp, a closed-circuit TV camera, a speaker for acoustic stimuli, and another speaker for white noise. The noise level from all sources averaged about 74 dB on the C scale.

The chair was equipped with two operant levers directly in front of the right and left hands, and a food receptacle was located on the top surface. During the study, the monkeys were food-deprived and maintained at about 92% of their free-feeding body mass. Colonic temperature was monitored continuously during each session with a nonperturbing probe.

A total of 328 sessions was devoted to the 1.3-GHz study, 133 sessions to the 5.8-GHz study, and 53 sessions to the 225-MHz study in that order, with about 70 days between the studies.

OTHER INFORMATION: Each monkey was trained in a Plexiglas chair to perform a vigilance or observing response task. In this task, the monkey was to press the lever in front of its right hand (an observing response), which produced either a 0.7-s low tone (860-1000 Hz) to signal that no food pellet will be delivered, or a high tone (1250-3703 Hz) lasting for up to 1.2 s, to signify the availability of a food pellet. The tones were sounded at a loudness of about 60 dB on the C scale. If the monkey pressed the lever in front of its left hand during sounding of the high tone (a detection response), the tone would stop and a pellet was delivered. A left-lever response at other times produced a 5-s interval during which right-lever presses yielded only the low tone. If the left lever was not pressed during 1.2 s of the high tone, the tone ceased and the reinforcement schedule would recycle. No tones occurred without a lever press, and right-lever presses during the presence of either tone had no consequences.

The low tone was sounded most frequently and the high tone was delivered randomly at an average of about once every 30 s. Reinforcement was at random intervals of about 1 min initially, and were shorter as the responses of the monkeys became more efficient. The monkeys were not exposed to RFR until several sessions of stable performance on the observing-response task had occurred.

For each frequency, each monkey (with a few exceptions) was exposed three times at each power density, usually sequenced in ascending order. However, all RFR-exposure sessions were followed with sham-exposure sessions. Sham-exposures were also given after weekends if behavior was not at baseline levels. About 100 sessions were necessary before all 5 monkeys responded consistently within and between sessions. Four of the monkeys reduced their rates of incorrect responses on the detection lever to low and stable levels. The fifth monkey, subject 10, made

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excessive numbers of incorrect detection responses throughout the study, which were sometimes greater than its observing-response rate.

Representative cumulative 1-hr records of observing-responses of one monkey, subject 13, during exposure to 1.3-GHz RFR at 26, 50, 70, and 90 mW/sq cm indicated reduction of the response rates at 50 mW/sq cm and higher, and that the rate reduction increased toward the latter part of each session. The cumulative records at the three frequencies also showed that the response patterns of the monkeys were erratic, an effect that was most pronounced at 225 MHz, at which the animals paused for as long as 15 min and often stopped responding completely for the last half of a session at 10 mW/sq cm.

As more definitive indices of behavioral changes than the individual cumulative records, the means and standard errors (SEs) of the ratio of observing-responses during RFR-exposure at each frequency to observing-responses during the previous sham-exposure session vs power density were displayed in Fig. 2 of the paper. For 225 MHz, the mean ratio decreased monotonically from 1.02 at 5 mW/sq cm to 0.75 at 10 mW/sq cm, with a large drop between 7.5 and 10 mW/sq cm; the differences from unity were statistically significant at 7.5 and 10 mW/sq cm.

For 1.3 GHz, the mean ratio was about unity up to 45 mW/sq cm, at which it increased to 1.1, a significant change that was primarily associated with the behavior of subject 10. At 50 mW/sq cm, the mean ratio was unity, in contrast with the representative cumulative record of subject 13, which indicated diminution of the response rate at this power density. At 63 mW/sq cm, the mean ratio dropped to 0.86, a significant change, and decreased only slightly at 93 mW/sq cm.

For 5.8 GHz, the mean ratio varied nonmonotonically above and below unity up to 140 mW/sq cm; these changes were relatively small, but some were statistically significant because the SEs below this power density were much smaller than those at the other frequencies. Again, however, the increases in mean ratio were due to the behavior of one monkey. At 140 and 150 mW/sq cm, the mean ratio was 0.92 and 0.90, respectively, both significant decreases. Also evident from Fig. 2 was the increase in threshold power density with frequency, i.e., about 7.5 mW/sq cm at 225 MHz, 63 mW/sq cm at 1.3 GHz, and 140 mW/sq cm at 5.8 GHz.

Exposure to 5.8 GHz at 150 mW/sq cm (the highest power density) also produced minor burns on the faces of three of the five monkeys, the worst occurring between the eyes and along the orbitonasal area. The erythema generally disappeared within a few days, except in one monkey that continued to irritate the burned skin by removing scabious material. Burns did not occur at 140 mW/sq cm (the behavioral threshold for this frequency) or at the highest power densities for the other frequencies.

The detection-response rate on the food lever was not consistently affected by exposure to RFR at any frequency. No effect was observed for 225 MHz or 5.8 GHz; for 1.3 GHz, a decreased response rate was

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occasionally observed, but only at 83 mW/sq cm or higher. However, plots of the mean ratio of detection-response latencies during RFR exposure to the latencies during sham exposure vs power density showed values slightly but significantly higher than unity at all frequencies and at most power densities. For each frequency, the mean ratio increased nonmonotonically with power density; the correlation coefficients were significant at the 5% level for 225 MHz and 1.3 GHz but not for 5.8 GHz. Also noteworthy were the successive decreases of the SEs for these ratios at 1.3 GHz, 5.8 GHz, and 225 MHz, the order in which these frequencies were used.

Another effect was on the postreinforcement pause (pause after a reinforced detection-response). For each frequency, the mean ratio of postreinforcement pause during RFR exposure to the pause during sham exposure was plotted vs power density. For 225 MHz, this ratio was about unity in the range 5-7.5 mW/sq cm, but rose to about 1.5 at 10 mW/sq cm, a significant change. For 1.3 GHz, the changes were both upward and downward and nonsignificant up to 63 mW/sq cm, at which the mean ratio was 1.3; the ratios decreased above 63 mW/sq cm to about 1.1 at 93 mW/sq cm, still a significant increase. For 5.8 GHz, the SEs were again much smaller than for the other frequencies; the only significant change was at 150 mW/sq cm, to about 1.06, a smaller increase than for the other frequencies.

The mean colonic temperature at the start of the 1-hr sessions was 38.6 deg C and generally increased by an average of 0.15 deg C during the sham-exposure sessions. The mean increases in temperature vs power density for each frequency were exhibited on linear scales in Fig. 5. No SEs were shown, but the author noted that they were typically 0.2 deg C or less. The results indicated that for 225 MHz, the temperature increases rose linearly from about 0.8 deg C at 5 mW/sq cm to about 2.1 deg C at 10 mW/sq cm. For 1.3 GHz, the temperature increases rose less than linearly, from about 0.4 deg C at 20 mW/sq cm to about 1.9 deg C at 93 mW/sq cm. For 5.8 GHz, the increases rose more gradually, from about 0.2 deg C at 10 mW/sq cm to about 1.0 deg C at 150 mW/sq cm. The author also referred to the somewhat different 2.45-GHz temperature curves previously obtained for squirrel monkeys (de Lorge, 1979) and rhesus monkeys (de Lorge, 1976); these 2.45-GHz curves were relatively flat initially and then accelerated dramatically as the temperature increases reached 1 deg C.

The equations for the curves of best fit were also shown in Fig. 5. The author stated: "The exponential curve at 225 MHz is distinctly different from the curves at 1.3 and 5.8 GHz." However, the curve displayed in Fig. 5 for 225 MHz was a straight line (with the linear scales used), whereas those for 1.3 and 5.8 GHz were logarithmic. Presumably, the quoted statement referred to equations of mean colonic temperatures, rather than mean temperature increases, vs power density.

Estimates of absolute thresholds for disruption of observing-response rates were made for each frequency on the basis of the following: The highest power density at which the SE bar overlapped the unity-ratio

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line was designated the "no-difference" estimate. The threshold power density for "obvious" difference in performance was defined as the value at which the SE bar did not overlap the unity-ratio line and a 10% or greater difference from the no-difference power density ratio was obtained. The resulting estimates were 8.1 mW/sq cm for 225 MHz, 57 mW/sq cm for 1.3 GHz, and 140 mW/sq cm for 5.8 GHz. The estimate for 2.45 GHz from de Lorge (1976) was 67 mW/sq cm.

For each frequency, the author also calculated the minimal power density associated with colonic-temperature increments of 1 deg C. From Fig. 5, the values at 225 MHz, 1.3 GHz, and 5.8 GHz were about 7.5, 40, and 150 mW/sq cm, respectively; from de Lorge (1976), the value at 2.45 GHz was about 63 mW/sq cm. These values show an almost linear relation between power density and frequency.

Estimates of SAR were derived from exposure of saline models to 225 MHz and 1.3 GHz (Lotz, 1982) and of flesh-simulating materials to 5.8 GHz (this study). These SARs were normalized by dividing them by the corresponding power densities. Formulas in Durney et al. (1978) were used for 2.45 GHz. The results, expressed in W/kg per mW/sq cm and displayed in Fig. 6, were about 0.4 for 225 MHz, 0.13 for 1.3 GHz, 0.07 for 2.45 GHz, and 0.03 for 5.8 GHz. The author noted that: "Although more energy per milliwatt of power was absorbed at 225 MHz [than at the other frequencies], substantially less absorbed energy was required to raise colonic temperature 1 deg C (2.5 W/kg)."

The author concluded: "Disruption of the observing-response, a behavior predicated on highly motivated performance, by microwave irradiation was closely related to increases in core temperature. The relationship is no doubt dependent upon various factors but, invariably, this behavior was not greatly disrupted unless body temperature increased by about 1 deg C, or unless an animal was suffering superficial burns or was bothered by facial skin irritation. Other aspects of operant behavior such as the detection-response rate and post-reinforcement pause failed to show this relationship."

He also stated: "The results of this study illustrate that predictions of biological effects based solely on power density are poor. Similarly, the information shown in Figure 6 reflecting the dependence of SAR on frequency demonstrates that predictions based on normalized whole-body energy absorption are not very useful." He noted, citing a contribution by D.R. Justesen (Fig. 7), that the ratio of highest-to-lowest threshold SAR, 2.6 (8.4/3.2), was much smaller than the ratio of the corresponding power densities, 17.5 (140/8), so SAR is a more efficient predictor than power density, but both are frequency dependent. He concluded, however, that a colonic temperature increase of about 1 deg C is a more reliable single index of behavioral disruption. His general conclusion was that the results of this study will allow predictions of possible behavioral alterations in other species, notably humans, during exposure to RFR at frequencies near and above resonance, especially if elevations of body temperature were used as indices.

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In the author's discussion, he speculated that the 225-MHz data reflect a resonance heating effect of the blood in the entire body, leading to extreme difficulty in thermoregulating because heated blood cannot be replaced with cooler blood. He also suggested that the results at 1.3 and 5.8 GHz illustrate normal thermoregulation, since limbs or skin are heated to a much greater extent than the interior of the head at these frequencies, citing Burr and Krupp (1980) and Olsen et al. (1980).

CRITIQUE: As noted by the author, this behavioral study of rhesus monkeys at 225 MHz, 1.3 GHz, and 5.8 GHz complements a similar study at 2.45 GHz (de Lorge, 1976). The results at all four frequencies provide a consistent and composite picture of alterations in performance of this nonhuman primate on a complex task during exposure to RFR and indicate the frequency dependence of the effects observed. He had also obtained comparable findings for squirrel monkeys exposed to 2.45-GHz RFR (de Lorge, 1979).

Absent was any discussion of the possible occurrence of the auditory-RFR effect with the pulsed RFR used at 1.3 and 5.8 GHz. The author presumably discounted this effect as a factor in the results, because the pulse repetition rates used (370 and 662 pps) were lower than the tones used in the behavioral paradigm.

The threshold power densities and SARs for the observed behavioral alterations and their association with colonic-temperature increases of about 1 deg C indicate the thermal basis of the effect, and the suggested use of colonic-temperature increase as an index in preference to power density or SAR is an idea that should be investigated further experimentally.

The occurrence of skin burns from exposure to 5.8 GHz at 150 mW/sq cm is probably a consequence of the relatively low penetration depth of RFR at this frequency (about 0.8 cm) as well as the high power density. It is interesting that this value is only a small percentage above the threshold for behavioral alteration (140 mW/sq cm). It also is likely that the increase in threshold with frequency is related to the inverse relationship between penetration depth and frequency.

Because primates are better surrogates for humans than the usually used lower species of laboratory animals, results with the latter could be misleading with regard to setting safety standards for human exposure to RFR. For example, de Lorge and Ezell (1980) exposed rats to 1.28 and 5.62 GHz, and obtained changes in observing-response rates with power-density thresholds of 15 and 26 mW/sq cm, respectively. These values were considerably lower than those for the rhesus monkeys at the comparable frequencies (57 mW/sq cm at 1.3 GHz and 140 mW/sq cm at 5.8 GHz). (Unfortunately, colonic-temperature rise could not be used as an index, because the temperatures of the rats were not measured in that study.)

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Milham, S., Jr.
OCCUPATIONAL MORTALITY IN WASHINGTON STATE: 1950-1979
DHHS (NIOSH) Publication No. 83-116, Contract No. 210-80-0088, U.S.
Department of Health and Human Services, National Institute for
Occupational Safety and Health, Cincinnati, Ohio   (Oct. 1983)

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AUTHOR ABSTRACT: The occupational and cause-of-death information on
429,926 Washington State male deaths for 1950-1979 and 25,066 female
deaths for 1974-1979 was analysed using an age and year-of-death
standardized proportionate mortality ratio program. A detailed cause-
of-death analysis (160 causes) is published for each of 219 occupational
categories for males and for each of 51 occupational categories for
females.

The occupational mortality findings are compared with those of the
Registrar General and with the published occupational mortality
literature. The Washington State mortality pattern is, in general,
consistent with both the Registrar General's results and with the
published literature. Some of the new occupational mortality findings
published in the 1950-1971 report and in this updated version have been
confirmed. Others warrant follow-up. These include a lung cancer
excess in workers at the ASARCO Tacoma copper smelter, increased
mortality due to multiple myeloma and pancreatic cancer in workers at
the Hanford atomic energy facility, and excess mortality due to cancer
of the pancreas, lymphoma, leukemia, and emphysema in aluminum workers.

New findings in this report are a leukemia increase in workers exposed
to electric and magnetic fields and a deficit of multiple sclerosis
deaths among outdoor workers.

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Study Type: Human Studies; Immunology and Hematology; Mutagenesis,
Carcinogenesis, and Cytogenetic Effects; IN VIVO; HUMAN
Effect Type: Increase in leukemia mortality rates in workers presumably
exposed occupationally to electric and magnetic fields
Frequency: Unknown (Implied as being DC through UHF)
Modulation: Unknown
Power Density: Unknown
SAR: Unknown

EXPOSURE CONDITIONS: Presumed to be occupational. Otherwise
unspecified.

OTHER INFORMATION: In a Letter to the Editor of the New England Journal
of Medicine, the author had previously reported an apparent increase in
the proportionate mortality ratio (PMR) for acute leukemia and for all
leukemia for persons occupationally exposed to electric and magnetic
fields in the State of Washington (Milham, 1982). The Letter provided

very little detail on specifics of the treatment of the data. The
present final contract report provides additional information.

Twenty microfiche negatives, which are provided with the 167-page
printed report, contain the detailed raw mortality data and calculated
PMRs for males by occupation, and for females by occupation. (The
"occupation" of each decedent was obtained from the statement on the
Washington State death certificate.) Additional information on
occupations ranked by PMR within each cause of death, and causes of
death with significantly (p<0.05) elevated or reduced PMRs by
occupation, both for males only, are also contained in the microfiches.
Eighty pages of the printed report describe occupation codes (common for
both men and women) used in filling out the death certificates,
occupation groupings for men, occupation groupings for women, an index
of occupations for men, and an index of occupations for women. The
analysis progresses from the raw mortality information through
progressive clustering of data in like occupational groupings,
presumably in order to obtain sufficient numbers in each cluster for
meaningful statistical analysis. The statistical method used by the
author is the PMR (proportionate mortality ratio), and a detailed
example of one such calculation is given in the report (p. 96). By
comparison, the Registrar-General's analysis uses the more common and
widely accepted standardized mortality ratio (SMR) (Lilienfield and
Lilienfield, 1980).

Sixty-three pages of the printed report contain one-paragraph
commentaries describing the mortality pattern as seen by the author in
each of the occupation groupings. There are 219 such commentaries for
males, 51 for females.

CRITIQUE: Some of these commentaries appear to be highly subjective and
to reflect the personal biases of the author. For example, the
following appears in the commentary on female mortality (p. 63):

"Waitresses
Occupation code 875
Total deaths 862

    Cancers of the esophagus, stomach, larynx, lung, cervix and uterus
unspecified have increased PMRs. Psychoses, pulmonary emphysema,
cirrhosis of the liver, motor vehicle accidents, and homicide have
mortality increases. Much of this mortality pattern may be due to life-
style patterns, i.e., smoking, drinking, and promiscuity."

Other commentaries seem to include some nonsignificant but elevated PMRs
because the author apparently believes they contribute to the overall
pattern of mortality that he believes is appropriate for that
occupation. For example (p. 54):

"Dietitians and Nutritionists
 Occupation code 073
 Total deaths 104

These women show a significant excess of malignant neoplasms of the digestive organs (PMR=254 based on 7 deaths) in the 20-64 age class. This is due to 4 deaths observed due to cancer of the pancreas to less than 2 expected. Malignant neoplasms of lymphatic and hematopoietic tissues (age 20-64) show a PMR of 476 based on 5 deaths, 3 of which were in the other lymphoma category. Diabetes mellitus had a PMR of 225 based on 5 deaths."

That is, of 104 total deaths in this occupation for women, the author has selected 17 and presented them as though dietitians and nutritionists might be expected to die more often of malignant neoplasms of the digestive organs and diabetes mellitus. The other 87 deaths have been ignored. This clearly demonstrates a subjective and selective bias in the author's application of the PMR analytical technique.

The analysis is carried one step further by the author by examining mortality by cause of death, showing occupational groupings with statistically significant elevations or reductions in PMR. There are several problems with some of the patterns that emerge in this treatment. For example, in the commentary on male mortality by occupation within cause-of-death groups is the following (p. 67):

"Malignant Melanoma of Skin (ICD 190)

Three of the four occupations with high PMRs (clergymen, school teachers, hotel managers) have no obvious relationship to outdoor work or exposure to sunlight. Navy and Coast Guard personnel, however, probably are exposed to sunlight."

This presumption that Navy and Coast Guard personnel have elevated PMRs for malignant melanoma of the skin because they are exposed to sunlight would seem to indicate a considerable bias on the part of the author. There is no indication as to why these personnel would spend more time in the sun than school teachers, for instance, other than the personal belief of the author that they do so.

The next step in the analysis by the author is to examine the mortality patterns of groups of selected occupations which appear to have similar environmental exposures. It is here, in one page of the entire report (p. 75), that categories of workers presumed to be occupationally exposed to magnetic and/or electrical fields are juxtaposed and PMRs for two categories of leukemia (acute leukemia, and all leukemia) are presented. There are 11 occupations: electrical engineers, electronic technicians, radio and telegraph operators, electricians, power and telephone linesmen, television and radio repairmen, motion picture projectionists, aluminum workers, streetcar and subway motormen, power station operators, and welders and flame cutters. Of the 22 categories for the two cases of leukemia by 11 occupations, there are 3 cases where the PMR is significant at the 0.01 level, plus 2 at the 0.05 level. The other PMRs, though elevated in 13 cases and depressed in 3 (with 1 the same), are not statistically significant. Those that are significant, electricians (both categories of leukemia), aluminum workers (both

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categories of leukemia), and power station operators (all leukemia only), represent 79 leukemia deaths from the total of 136 leukemia deaths actually observed in these occupations. The excess deaths (observed minus expected) for these three occupations number 28. At this point we should quote the author on the PMR technique (p. 5):

"The major flaw of the proportionate mortality ratio (PMR) is that it says nothing about total force of mortality for a given occupation... All occupations have a total PMR of 100. Also, since the cause-of-death specific PMRs must sum to 100, a very high or low PMR in a common cause-of-death group will affect the other PMRs for that occupation."

In other words, the 5 significantly high PMRs mentioned above might, by virtue of the technique itself, arise because other PMRs in three of the 11 occupations are abnormally low. This does not give great credence to the author's claim that the increased PMRs for all leukemia and for acute leukemia are associated with exposure to electric and magnetic fields. The other point to be made is that there must be a dose-response relationship for a cause-and-effect relationship to hold in this and other epidemiologic studies. Such a relationship is at best unproven here. In the absence of exposure data for the individuals, or even of the occupations, it is only an assumption that persons in these occupations actually do experience greater exposure to electrical and magnetic fields than do those in other occupations. For example, electricians, the occupation with the largest number of leukemia deaths (51), actually spend a large part of their time working on circuits that are not energized.

Perhaps the strongest criticism that can be levelled against the present study as a whole is that it demonstrates an approach that statisticians commonly refer to as "data mining." A very large data base is "picked over" for "nuggets" of (locally) statistically significant items, which are then assembled to show purported relationships. Unfortunately, there is no a priori hypothesis that is being tested. The normal statistical methodology is reversed---statistical significance is found and then the hypotheses are formulated. Results from such an approach are generally considered not to carry much weight.

In summary, when viewed in the context of the complete report of occupational mortality in Washington State, the claim that workers exposed occupationally to electric and magnetic fields have increased incidence of all leukemia and acute leukemia is seen not to be a particularly strong one. The methodological approach does not meet the normal criteria for the statistical testing of hypotheses---there is no a priori hypothesis being tested. The commentaries on patterns of mortality underlying different occupations from which the groups such as the electrical and magnetic field workers were selected seem to show a personal bias by the author, and the proportionate-mortality-ratio technique has analytical problems that could cause an apparent increase in the PMR in one cause-of-death category to arise from an abnormally low PMR in one or another category. The relationship between leukemia and exposure to electric and magnetic fields should therefore be treated

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autiously until better analytical techniques are employed and better
xposure information is available.

)f course, these criticisms apply equally to all other purported cause-
ind-effect relationships claimed in the report for other agents and
)ccupations.

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MILHAM

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ssions in the waveguides. Drinking water was removed from the home iges 24 hr prior to the first session. On session days 1, 2, and 3, ie rats were inserted in the waveguides for 45 min with the RFR source ι "standby." At this time, a bottle containing a 10% sucrose (w/v))lution was inserted in each waveguide and the amount of solution)nsumed during the remaining 45 min was measured. The procedure on ᴜ., was the same except that half the rats (24) selected randomly (and lindly to the investigator) were exposed to the RFR and the other half ηre sham-exposed for the full 90 min. The procedure on days 5-7 was ie same as for days 1-3 except that a solution of 10% sucrose (w/v) + 5% ethanol (v/v) was used. (The sucrose served to render the ethanol ore palatable.) On day 8, half the rats (group I, randomly selected) ere exposed to RFR and the other half (group II) were sham-exposed for he 90 min and the amounts of sucrose-ethanol solution consumed during his period were determined. (Each bottle was fitted with choke ections that decoupled the rat from the RFR.) On day 9, group I was ham-exposed, group II was RFR-exposed, and fluid consumption was noted.

THER INFORMATION: The RFR-exposure parameters were the same as those eported to have yielded significant effects on the actions of ιpomorphine, amphetamine, and morphine (Lai et al., 1983) and on ιentobarbital-induced hypothermia (Lai et al., 1984a). The SAR of 0.6 '/kg was determined calorimetrically and corresponded to 1 mW/sq cm of :ircularly polarized RFR; its equivalent in power density of linearly)olarized RFR, 3-6 mW/sq cm, was estimated from Durney et al. (1978).

:olonic-temperature-response curves were compared by the nonparametric ịtatistical method described by Krauth (1980), in which the response :urve of each rat was approximated by orthogonal polynomials and the ːero-order orthogonal coefficients from the different treatment groups ᵥere compared by chi-square analysis. The data on fluid consumption for ːhe various sessions were compared by the two-tailed, paired t-test.

[n the ethanol-hypothermia experiment, the mean colonic temperatures and ịEMs of the RFR- and sham-exposed rats immediately after exposure were 38.2 +/- 0.1 and 38.3 +/- 0.1 deg C, respectively, a nonsignificant lifference. Ataxia developed within 5 min of ethanol injection, but the righting reflex remained intact. The mean colonic temperature changes (+/- SEMs) vs time after ethanol injection for the two groups, presented ịn Fig. 1 of the paper, indicated that hypothermia occurred in the RFR ịroup at a slower rate than in the sham group. For example, the mean ːemperature depressions at 15 min after injection were about 0.4 and 0.9 ịeg C for the RFR and sham groups, respectively, a significant lifference; the corresponding depressions at 60 min were about 1.5 and ι.8 deg C, also a significant difference; at 90 min, the depressions ᵥere about 1.9 deg C for both groups and did not differ significantly [rom one another at subsequent times.

ſhe sucrose and ethanol-sucrose consumptions for the 9 daily sessions ᵥere presented in Table 1. For days 1, 2, and 3, during which all 48 ſats were sham-exposed and offered the sucrose solution, the mean :onsumption values increased monotonically and significantly: 29.0 +/-

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Lai, H., A. Horita, C.-K. Chou, and A.W. Guy
ETHANOL-INDUCED HYPOTHERMIA AND ETHANOL CONSUMPTION IN THE RAT ARE
AFFECTED BY LOW-LEVEL MICROWAVE IRRADIATION
Bioelectromagnetics, Vol. 5, No. 2, pp. 213-220 (1984b)

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AUTHOR ABSTRACT: Microwave irradiation of rats by circularly polarized,
2,450-MHz, pulsed waves (2-microsecond pulses; 500 pps) was performed in
waveguides to determine effects on ethanol-induced hypothermia and on
ethanol consumption. Rats injected intraperitoneally with ethanol (3
g/kg in a 25% v/v water solution) immediately after 45 min of microwave
irradiation exhibited attenuation of the initial rate of fall in body
temperature, which was elicited by the ethanol, but exhibited no
significant difference in maximal hypothermia as compared with that of
sham-irradiated rats. Microwave irradiation did not affect the
consumption of a 10% sucrose (w/v) solution by water-deprived rats.
However, it enhanced the consumption of a solution of 10% sucrose (w/v)
+ 15% ethanol (v/v) by water-deprived animals. These results were
obtained at a specific absorption rate (SAR) of 0.6 W/kg, which rate of
energy dosing would require a power density of 3-6 mW/sq cm if exposure
of the animals had occurred to a 12-cm plane wave.

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Study Type: Multiagent Interactions, Metabolism and Thermoregulation,
Nervous System, Physiology and Biochemistry; IN VIVO; RAT
Effect Type: RFR-induced alterations of ethanol-induced hypothermia and
ethanol consumption
Frequency: 2.45 GHz
Modulation: 2-microsecond pulses at 500 pps (0.001 duty)
Power Density: 1 mW/sq cm (circularly polarized); equivalent to 3-6
mW/sq cm of linearly polarized RFR
SAR: 0.6 W/kg

EXPOSURE CONDITIONS: Acute RFR- and sham exposures of male Sprague-
Dawley rats (250-300 g at the start) were performed concurrently for
each part of the study in waveguide systems (one per rat) developed by
Guy et al. (1979), all housed in a room at a mean ambient temperature of
22.0 deg C (+/- 0.1 SEM). The exposures were conducted blind, i.e., the
investigator did not know which treatment was given any rat.

For the ethanol-hypothermia experiment, 15 rats were RFR-exposed and 14
rats were concurrently sham-exposed for 45 min. Immediately after
exposure, each rat was removed from its waveguide, its colonic
temperature was measured, and it was injected IP with 3 g/kg of ethanol
(in a 25% v/v water solution). The rats were then housed 6 to a cage
and their colonic temperatures were measured with a thermistor probe
inserted and removed at 15-min intervals for 120 min.

In the ethanol-consumption study, 48 rats were given 9 daily 90-min

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DRUG-RFR
HYPCTHERMIA
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THERMOREGULATION

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dependent findings were due to the differences in localized energy depositions for the two orientations, which could yield differences in drug metabolism or kinetics.

CRITIQUE: Other than the minor comment above about the faster rate of recovery of the posterior-RFR group from the hypothermia, the results of this investigation appear to be straightforward. However, in the earlier investigation of the effects of the same kind and level of RFR on the actions of apomorphine, amphetamine, and morphine on the Sprague-Dawley rat (Lai et al., 1983), the authors remarked that"...since albino rats were used in our experiments and albino animals have been shown to have aberrant metabolic and neurological functions [Creel, 1980], it may be interesting to repeat some of these experiments using hooded rats, eg, Long-Evans." Since Sprague-Dawley rats were also used in the present investigation, this remark seems applicable here as well.

As in the earlier investigation, the peak power density of the RFR pulses was at least 1·W/sq cm, within the range of perception of the pulses as sound. Thus, it is possible that the conscious rats in experiment 1 perceived the pulses. However, it would be difficult to connect such perception with the RFR-related differences in the pentobarbital-induced hypothermia and analepsis therefrom reported.

The quotation of the authors' remark above about the difference in depth of the hypothermia induced in the sham-exposed rats in the two experiments appears to be in error: the -3.0 deg C at 90 min after injection for experiment 1 is correct; however, the corresponding time in experiment 2 was not 30 but 75 min after exposure, at which time the mean temperature depression was also about 3 deg C. Moreover, in neither case did the 90-min point correspond to the time of maximal hypothermia, which occurred at 75 min in experiment 1 and 45 min in experiment 2 (both reckoned from injection time). The temperature depressions for the sham groups at these times were about 3.2 and 4.5 deg C, respectively. Thus, not only were the maximal depressions significantly different, but so were their times of occurrence. The reasons for these differences are not clear. However, data on sham-exposed animals administered saline instead of pentobarbital might have more clearly delineated such subtle non-RFR factors.

A similar investigation was conducted by Lai et al. (1984b) on the effects of RFR on ethanol-induced hypothermia and ethanol consumption.

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rate and extent of fall in colonic temperature between microwave- and
sham-exposed animals indicates that microwaves do not affect drug
absorption and distribution at least to the sites of action. However,
effect on drug metabolism cannot be discounted. Even though no
significant effect on colonic temperature was detected in our irradiated
animals, focal heating of areas of the brain or body leading to altered
drug metabolism cannot be ruled out."

Regarding their second series, they stated: "In our second study, we
found that microwave exposure attenuated the fall in colonic temperature
in pentobarbital-anesthetized animals. This is probably due to
absorption of energy from the radiation. Both anterior- and posterior-
exposed rats showed the same degree of attenuation, which is consistent
with the dosimetry finding that similar amounts of radiation energy are
absorbed by the whole body in both orientations of exposure. The fact
that microwave irradiation affects the core temperature in anesthetized
but not in conscious rats, suggests that in the conscious rats a
compensatory thermoregulatory mechanism is functioning during the
exposure to maintain a constant core temperature...by increasing heat
loss or decreasing heat production... However, during pentobarbital
anesthesia the rat is rendered poikilothermic and the thermal effect of
microwaves is seen as an attenuation of the hypothermia... A similar
phenomenon has also been reported in animals after treatments with other
drugs that disturb thermoregulation. Significantly, Putthoff et al.
(1977) have reported a greater microwave-induced increase in body
temperature in rats treated with sodium salicylate or cortisone.
Recently, Smialowicz (1983) also reported increase in colonic
temperature in rodents whose thermoregulatory mechanisms were impaired
by treatment with serotonin or lipopolysaccharides, and irradiated with
microwaves at SARs less than 1 W/kg, which were nonthermogenic in normal
animals."

The authors pointed out that: "...the extents of pentobarbital-induced
hypothermia in the sham-irradiated rats are different in the two
experiments. In experiment 1, the average fall in colonic temperature
for the sham-irradiated rats at 90 min after pentobarbital injection was
-3.0 +/- 0.2 deg C (n=13), whereas the temperature change at the same
time after injection (ie, 30 min after exposure) for the sham-irradiated
animals in experiment 2 was -4.2 +/- 0.2 deg C (n=20) (significantly
different at P<.001, two-tailed Student's t-test). This difference was
probably due to differences in experimental procedures between the two
experiments. In experiment 1, thermister [sic] probes were left
inserted into the rats after the drug treatment and during the course of
the study, whereas in experiment 2, the animals were left undisturbed
during the 45-min exposure period which started at 15 min after the drug
treatment. Owing to this difference, caution should be taken in
comparing the results of the two experiments."

Another finding commented on by the authors was the smaller maximal
colonic-temperature depression and the earlier recovery time of the
righting reflex for the posterior-RFR group relative to the values for
the anterior-RFR and sham groups. They surmised that these orientation-

In the second series, the baseline mean colonic temperatures of the injected rats before RFR- or sham exposure in the anterior and the posterior orientation were all 37.9 +/- 0.1 deg C. For the groups sham-exposed in the two orientations, there was no significant difference in their mean colonic temperatures immediately after sham exposure, so their results were pooled. The values for the anterior-RFR and posterior-RFR groups and for the combined sham group immediately after exposure were 34.6 +/- 0.1 (12 rats), 34.7 +/- 0.2 (10 rats), and 34.1 +/- 0.1 deg C (20 rats), respectively. The mean temperatures of the two RFR groups did not differ significantly; however, the values for both were significantly higher than for the sham group.

Plots of the mean change in colonic temperature (from values before injection) vs time after exposure were exhibited in Fig. 2 for the three groups. (The values above were for 0 min.) All three groups attained maximal hypothermia 30 min after exposure (45 min after injection). The temperature changes at that time for the posterior-RFR, anterior-RFR, and sham groups were about -3.8 +/- 0.38, -4.2 +/- 0.22, and -4.5 +/- 0.15 deg C, respectively. Only the difference in mean depressions for the posterior-RFR and sham groups was significant.

From 30 to 90 min, all three groups showed recovery toward baseline temperatures, with no significant differences at corresponding times between the anterior-RFR and sham groups. However, the temperatures of the posterior-RFR group were significantly higher than those of the other groups at corresponding times during that interval, i.e., the posterior-RFR group recovered from the hypothermia earlier (but not faster as stated in the abstract; the mean slopes of the plots for the three groups during this interval were about the same, but the maximal mean depression for the posterior-RFR group was smaller than for the other two groups). In addition, the rats in that group recovered their righting reflex more quickly (26 +/- 4, 45 +/- 5, and 50 +/- 4 min for the posterior-RFR, anterior-RFR, and sham groups, respectively; the difference between the latter two groups was not significant).

In their discussion, the authors noted that Wangemann and Cleary (1976) had reported shortening of pentobarbital narcosis in rabbits exposed to 2.45-GHz RFR at 5, 10, and 25 mW/sq cm and that Blackwell (1980) showed that mice anesthetized with hexobarbital regained their righting reflex faster after exposure to 2.45-GHz RFR at 25 or 50 mW/sq cm, with the latter effect not due to stress because the RFR-exposed mice had lower corticosterone levels than the controls. They also surmised that the power densities used in both studies were thermogenic, and therefore that the analeptic effect of the RFR could be a thermally mediated alteration of the pharmokinetics of the drugs.

For comparison, the authors stated (evidently regarding their first series): "In our study, when the effect of pentobarbital was studied after exposure, we found that microwaves affected the recovery rate from pentobarbital-induced hypothermia without affecting the initial rate and the maximal fall in colonic temperature. The cause of this effect is not readily known. However, the fact that there is no effect on initial

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the drug study did not know which treatment was given any rat. Colonic temperatures were taken immediately after exposure, the probe was removed, and each rat was injected IP with pentobarbital sodium at a dose sufficient to induce surgical anesthesia. After the rat lost its righting reflex, the probe was reinserted, colonic temperature was recorded at 15-min intervals for 150 min, and the time interval after injection to regain the righting reflex was noted.

In the second series, baseline colonic temperatures were measured and the rats were injected with pentobarbital. Fifteen min later, by which time all the rats had lost their righting reflex, 12 rats were exposed anteriorly (head toward source) and 10 rats posteriorly (rear toward source) for 45 min to the RFR in waveguides, concurrently with 10 rats sham-exposed in each orientation. Colonic temperatures were recorded for 90 min after exposure and the time interval after exposure to regain the righting reflex was noted.

OTHER INFORMATION: The exposure parameters were the same as those used by Lai et al. (1983), for which they reported significant effects of the RFR on the actions of apomorphine, amphetamine, and morphine. The SAR of 0.6 W/kg corresponded to 1 mW/sq cm of circularly polarized RFR; its equivalent in power density of linearly polarized RFR, 3-6 mW/sq cm, was estimated from Durney et al. (1978).

Colonic-temperature-response curves were compared by the nonparametric statistical method described by Krauth (1980), in which the response curve of each rat was approximated by orthogonal polynomials and the zero-order orthogonal coefficients from the different treatment groups were compared by chi-square analysis. Student's two-tailed t-test was used to compare colonic temperatures at corresponding times and to compare times for regaining the righting reflex.

In the first series, the (conscious) rats did not exhibit any preferred orientation during RFR exposure and there was no significant difference in mean colonic temperature between the RFR- and sham-exposed rats immediately after exposure (37.8 +/- 0.1 deg C SEM for both groups). The authors noted that in a separate experiment with 27 conscious rats exposed to RFR and 27 conscious rats sham-exposed for 45 min, there were no significant alterations of colonic temperature during that period or differences between groups. Mean changes in colonic temperature (+/- SEMs) vs time after pentobarbital injection, plotted for each group in Fig. 1 of the paper, showed that both groups reached maximal hypothermia (about -3 deg C) at 75 min. At corresponding times until 90 min after injection, the mean temperature depressions for the sham group were larger than for the RFR group, at which time the two plots intersected, but none of the differences in mean depressions between the groups up to 105 min was significant. At corresponding times from 105 to 150 min, the mean depressions for the RFR group were all significantly larger (p<0.05) than for the sham group, i.e., recovery of the RFR group from the hypothermia was slower. In addition, the mean recovery time of the righting reflex for the RFR group was significantly longer (p<0.05) than for the sham group (100 +/- 3 min vs 90 +/- 3 min).

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Lai, H., A. Horita, C.-K. Chou, and A.W. Guy
EFFECTS OF ACUTE LOW-LEVEL MICROWAVES ON PENTOBARBITAL-INDUCED
HYPOTHERMIA DEPEND ON EXPOSURE ORIENTATION
Bioelectromagnetics, Vol. 5, No. 2, pp. 203-211 (1984a)

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AUTHOR ABSTRACT: Two series of experiments were performed to study the
effects of acute exposure (45 min) to 2,450-MHz circularly polarized,
pulsed microwaves [1 mW/sq cm, 2-microsecond pulses, 500 pps, specific
absorption rate (SAR) 0.6 W/kg] on the actions of pentobarbital in the
rat. In the first experiment, rats were irradiated with microwaves and
then immediately injected with pentobarbital. Microwave exposure did
not significantly affect the extent of the pentobarbital-induced fall in
colonic temperature. However, the rate of recovery from the hypothermia
was significantly slower in the microwave-irradiated rats and they also
took a significantly longer time to regain their righting reflex.

In a second experiment, rats were first anesthetized with pentobarbital
and then exposed to microwaves with their heads either pointing toward
the source of microwaves (anterior exposure) or pointing away (posterior
exposure). Microwave radiation significantly retarded the
pentobarbital-induced fall in colonic temperature regardless of the
orientation of the exposure. However, the recovery from hypothermia was
significantly faster in posterior-exposed animals compared to those of
the anterior-exposed and sham-irradiated animals. Furthermore, the
posterior-exposed rats took a significantly shorter time to regain their
righting reflex than both the anterior-exposed and sham-irradiated
animals.

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Study Type: Multiagent Interactions, Metabolism and Thermoregulation;
IN VIVO; RAT
Effect Type: Alterations of pentobarbital-induced hypothermia by
exposure of unrestrained rats to circularly polarized RFR before
injection and by exposure of rats anteriorly and posteriorly to the RFR
after anesthetization with pentobarbital
Frequency: 2.45 GHz
Modulation: 2-microsecond pulses at 500 pps (0.001 duty)
Power Density: 1 mW/sq cm (circularly polarized); equivalent to 3-6
mW/sq cm of linearly polarized RFR
SAR: 0.6 W/kg

EXPOSURE CONDITIONS: In the first of two series, 13 unanesthetized,
unrestrained male Sprague-Dawley rats (250-300 g) were exposed for 45
min to circularly polarized pulsed RFR at a whole-body SAR of 0.6 W/kg,
and 13 rats were sham-exposed, all in individual waveguide systems
developed by Guy et al. (1979), in a room at a mean ambient temperature
of 22.0 deg C (+/- 0.1 SEM). Six rats each were RFR- and sham exposed
concurrently at a time in blind fashion, i.e., the experimenter who did

MERRITT
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CALCIUM
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0.12-2.9

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control series of experiments for the in-vivo case did show that the concentration of 45-Ca++ in whole brain decreased by 30% during the 20-min exposure period. The only logical way that such a decrease could occur under the in-vivo experimental conditions described was by uptake into the bloodstream and thence to the rest of the body. If 45-Ca++ was present in the blood, it could have caused erroneous readings in whole-brain liquid-scintillation spectroscopy. Perfusion of the animals with saline following euthanasia might have been advisable.

In summary, the authors found no difference in 45-Ca++ concentrations between exposed and sham-exposed rat brain tissue for both in-vitro and in-vivo cases, and concluded that net 45-Ca++ efflux was not altered by pulse-modulated RFR under the conditions used in the study. Comparison of these negative findings with other studies reporting effects with amplitude-modulated RFR is rendered difficult because of the large differences between the studies in experimental procedures, carrier frequencies, and analytical techniques.

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Bioelectromagnetics, Vol. 1, No. 1., pp. 35-43 (1980)

Noble, E.P. et al.
A SIMPLE AND RAPID METHOD FOR INJECTING 3-H NOREPINEPHRINE INTO THE
LATERAL VENTRICLE OF THE RAT
Life Sci., Vol. 6, pp. 281-291 (1967)

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CRITIQUE: This report, in the form of a Brief Communication, describes an attempt to see whether previously reported RFR-induced changes in calcium efflux using amplitude-modulated waveforms (Adey, 1980; Bawin et al., 1975; Blackman et al., 1979; Blackman et al., 1980) might also be seen with pulse-modulated waveforms. No such RFR-induced changes were found. However, there were numerous differences between this study and those of other authors reporting effects, in addition to the stated difference of using pulsed modulation instead of amplitude modulation:

1) The carriers used were 1, 2.06, and 2.45 GHz whereas the highest frequency used in the other studies was 450 MHz.

2) 45-Ca++ loading of the brain was via injection into the right ventricle of the brain of the intact animal whereas the other studies had used external bathing media containing 45-Ca++. The dynamics of regional uptake of 45-Ca++ by this intraventricular method were not described, but measurements of calcium diffusion in the other studies indicated that their reported RFR-induced changes were probably obtained from the outer mm or so of cortical tissue. Not reported was whether the intraventricular technique loaded cortical tissue. Indeed, it is not clear whether this technique may have resulted in passage of the 45-Ca++ from the cerebrospinal fluid directly into the bloodstream in addition to the assumed perfusion from the cerebrospinal fluid into brain tissue. No measurements were reported for 45-Ca++ levels in the blood.

3) Also not reported was whether only the right hemisphere or whether both hemispheres were used to provide tissue samples for in-vitro irradiation. Injection into the right hemisphere might have provided asymmetrical loading. For the in-vivo exposures, apparently the whole brain was solubilized. It is unclear what the effect of any 45-Ca++ still remaining in the ventricular fluid might have had on the liquid-scintillation-spectroscopy results. The intraventricular injection technique, originally developed for injecting tritiated norepinephrine into the lateral ventricle of the rat, would seem to require additional characterization for the present application.

4) As in other studies on in-vitro samples, the present study found great variability in the liquid-scintillation-spectroscopy results. The other studies used the technique of normalizing the results of an RFR-exposed-brain half to the results of a matched, sham-exposed-brain half to reduce the overall variability. Because of the technique for loading the brain with 45-Ca++ in the present study, this analysis technique was not possible.

5) Other studies using both in-vivo and in-vitro techniques have reported that the alterations in calcium efflux have only been detectable as alterations in the concentration of 45-Ca++ in the incubating medium, not in solubilized brain tissue itself. Although the present paper reported that measurements had been made on samples of the bathing medium for the in-vitro case, no such results were given. The only results given were for solubilized brain tissue. However, a

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OTHER INFORMATION: For both in-vitro and in-vivo cases, brain tissue was loaded with 45-Ca++ by injection directly into the right lateral ventricle of ether-anesthetized male Sprague-Dawley rats (175-225 g) using the technique of Noble et al. (1967).

For the in-vitro cases, rats were euthanized by cervical dislocation and the brain quickly removed. A coronal cut was made about 5 mm behind the frontal border of the cortex followed by a horizontal cut, yielding about one quarter of the cerebrum. The individual samples were washed with physiologic medium and stripped of the pia mater prior to being placed in 50-ml beakers containing 2 ml of the same medium. Immediately after exposure or sham-exposure, a 0.5-ml aliquot of the incubating medium was transferred to a counting vial and 9 ml of Dimilume scintillation counting fluid was added. The tissue samples were gently washed with fresh medium, transferred to counting vials containing 2 ml of Soluene tissue solubilizer, and digested overnight at 37 deg C. Then, 8 ml of Dimilume was added. Next, liquid scintillation spectroscopy was performed on the incubating medium and, separately, the dissolved tissue samples.

No results were given for the incubating medium. For the dissolved tissue samples, there were no statistically significant differences between irradiated and sham-irradiated samples in terms of disintegrations per minute per gram of tissue for any of the exposure conditions.

For the in-vivo cases, the rats were euthanized by cervical dislocation after whole-body exposures and the brains were quickly removed, rinsed in physiologic medium, blotted dry, weighed, and solubilized in Soluene. An aliquot of the solubilized tissue was transferred to a counting vial containing Dimilume and assayed for 45-Ca++ by liquid scintillation spectroscopy.

Several statistical tests were performed on the 17 treatment combinations (4x4 irradiation, 1 sham-irradiation). There was no statistically significant difference between the sham and the combined irradiation groups, nor was there any difference between the sham and the individual irradiation groups at the 0.05 confidence level.

To measure the change in calcium-ion concentration that occurred in the brain during the 20-min period following the 2-hr postinjection period, a control series of experiments was conducted on 12 animals. These were treated in the same manner as the sham-exposed rats, i.e., they were injected intraventricularly with 45-Ca++ and allowed to stabilize for 2 hr. However, their brains were assayed immediately after the 2-hr period to ascertain the amount of 45-Ca++ at the beginning of the 20-min period used for the sham- and RFR-exposed rats. This experiment yielded a value of 0.944 +/- 0.033 ng-atoms/g of brain tissue (mean +/- SD). For the group of 12 animals sham-exposed for 20 min, the value was 0.659 +/- 0.156 ng-atoms/g, indicating that there was a net efflux of 0.285 ng-atoms/g during the 20-min period.

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Merritt, J.H., W.W. Shelton, and A.F. Chamness
ATTEMPTS TO ALTER 45-CA++ BINDING TO BRAIN TISSUE WITH PULSE-MODULATED
MICROWAVE ENERGY

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AUTHOR ABSTRACT: Rat brain tissue, loaded with 45-Ca++ by
intraventricular injection was exposed in vitro to pulse-modulated 1-GHz
(SAR of 0.29 or 2.9 W/kg) or 2.45-GHz radiation (SAR = 0.3 W/kg), and in
vivo to 2.06-GHz radiation (SAR of 0.12 to 2.4 W/kg). There were no
significant differences in efflux of 45-Ca++ between the microwave- and
sham-irradiated groups.

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Study Type: Nervous System; IN VITRO, IN VIVO; RAT
Effect Type: Alteration of calcium binding in rat brain tissue as a
result of exposure to RFR pulse-modulated at frequencies reported to be
effective with amplitude modulation.
Frequency: 1, 2.06, and 2.45 GHz
Modulation: 1 GHz: 20-ms pulses at 16 pps; 2.06 GHz: CW or 10-ms pulses
at 8, 16, or 32 pps; 2.45 GHz: 20-ms pulses at 16 pps
Power Density: 1 GHz: 1 or 10 mW/sq cm; 2.06 GHz: 0.5, 1.0, 5.0, or
10.0 mW/sq cm; 2.45 GHz: 1 mW/sq cm
SAR: 1 GHz: 0.29 or 2.9 W/kg; 2.06 GHz: 0.12, 0.24, 1.2, or 2.4 W/kg;
2.45 GHz: 0.3 W/kg

EXPOSURE CONDITIONS: For the in-vitro experiments, six individual
samples of brain tissue were exposed (or sham exposed) simultaneously to
RFR at 1 or 2.45 GHz. Each sample was contained in a 50-ml beaker
containing 2 ml of physiologic medium. The samples were maintained at
37 deg C in a Plexiglas and Styrofoam shaking water bath placed 1 m
beneath a standard gain horn. Radiation was produced by either an MCL
Model 15022 (for 1 GHz) or a Cober Model 1831 (for 2.45 GHz) RFR
generator. Incident power densities at sample positions were measured
with a Narda Microwave Corp. Model 8316B RF monitor and 8323 probe. The
method of measuring the SARs of the samples was not described.

For whole-animal exposures, the rats were injected intraventricularly
with 45-Ca++ and 2 hr later were placed in Plexiglass and Styrofoam
holders. The animals were exposed for 20 min to 1 of 17 different
combinations of power density and pulse repetition rate. Each rat was
assigned randomly to an exposure condition, and exposure conditions were
presented randomly to eliminate time-of-day effects. Animals were
oriented with their long axes parallel to the E-field, 4.5 m in front of
a horn antenna in a climate-controlled anechoic chamber. The 2.06-GHz
RFR was produced by a Cober Model 2852 transmitter. Incident power
densities were measured as for the in-vitro case. SARs were measured in
muscle-equivalent rat models via calorimetric techniques.

2.4, 46.5 +/- 3.1, and 67.0 +/- 2.1 ml/kg, respectively. On day 4, when half the rats were exposed to the RFR and the other half were sham-exposed for 90 min, the respective values were 70.6 +/- 2.8 and 71.6 +/- 2.6 ml/kg; these did not differ significantly from each other or from the day-3 value. Thus, exposure to RFR had no apparent effect on sucrose consumption.

For days 5, 6, and 7, during which all 48 rats were sham-exposed and offered the sucrose-ethanol solution, the mean consumption values were 26.2 +/- 1.0, 34.2 +/- 1.6, and 30.0 +/- 1.9 ml/kg; the changes were clearly nonmonotonic with time. For day 8, when group I (24 rats) was RFR-exposed and group II (24 rats) was sham-exposed, the respective values were 37.6 +/- 1.8 and 30.5 +/- 1.9 ml/kg; the latter value did not differ significantly from that for day 7, but the corresponding value for the RFR group was significantly higher (about 23%) than the day-7 value. For day 9, when group II was RFR-exposed and group I was sham-exposed, the group-II value was 38.9 +/- 2.1 ml/kg and the group-I value was 30.4 +/- 1.9 ml/kg; again, consumption increased (about 28%) for the group exposed to RFR on that day. However, consumption by the group sham-exposed on day 9 returned to the day-7 value, so the increase in consumption associated with RFR exposure of this group on day 8 was a temporary effect.

Regarding the ethanol-hypothermia experiment, the authors noted: "Our results show that acute microwave irradiation at 0.6 W/kg delays the effect of ethanol on body temperature. The mechanism of the effect is not known. Ethanol renders an animal poikilothermic, thus inducing hypothermia when the ambient temperature is lower than body temperature [Myers, 1981]. It is unlikely that microwaves retard the action of ethanol by affecting the entry of ethanol into the brain, since ethanol readily permeates the blood-brain barrier and is rapidly distributed in brain tissue. A possible explanation is that microwaves affect neural thermoregulatory mechanism(s), which in turn retards the heat-loss processes triggered by ethanol."

They also stated: "The results from the second experiment show that microwaves enhance consumption of a sucrose + ethanol solution without affecting consumption of a sucrose solution. Because sucrose is similar in caloric value to ethanol, and because its consumption was unaffected by microwave irradiation, it would appear that the microwave-induced increase in ethanol consumption was not due to a shift in caloric requirement of the rats." They offered several hypotheses regarding the apparent alterations of ethanol action by RFR observed in this study, but concluded that further research would be necessary to elicit specific mechanisms.

CRITIQUE: The procedures used in the two experiments, the statistical treatment of the data, and the experimental findings reported appear sound. Open to question, however, is the relevance of the results of the ethanol-hypothermia experiment to possible hazards to humans of RFR-ethanol interactions, because of the high ethanol dose used. On a body-weight basis, injection with 3 g/kg of ethanol in a 25% v/v water

solution is equivalent to a 700-ml dose of 50-proof liquor for a 70-kg human, clearly a substantial "slug" of alcohol.

In the second experiment, the mean consumption of sucrose alone on day 3 was 67.0 ml/kg, whereas the day-3 consumption of sucrose-ethanol was 30.0 ml/kg, indicating that even when water-deprived, the rats still found the sucrose-ethanol solution sufficiently distasteful to restrict its consumption. On the other hand, their higher consumption of the sucrose-ethanol solution under RFR- than sham-exposure may be an indication that the additional heat produced by the RFR induced the water-deprived rats to drink more despite their aversion to ethanol. This point is supported by the following sentence (in one of the authors' hypotheses): "In another experiment, we found that rats absorbed a considerable amount of microwave energy (about 0.16 J/g) when irradiated in the pulsed, 1-mW/sq-cm field for 45 min [Lai et al., 1984(a)]. However, the animals did not show any change in body temperature immediately after exposure; the implication is that they were actively dissipating the thermalized microwave energy." It should be noted that by calculation, the amount of energy absorbed in 45 min at an SAR of 0.6 W/kg is 1.6, not 0.16 J/g, which strengthens the point made. It is also interesting that 0.6 W/kg is about 10% of the basal metabolic rate for a medium (320-g) rat (Durney et al., 1978, p. 47).

An investigation was also conducted by Lai et al. (1984a) on the effects of the same kind and level of RFR on pentobarbital-induced hypothermia. As in that investigation, the peak power density of the RFR pulses was at least 1 W/sq cm, within the range of perception of the pulses as sound. Thus, it is possible that the rats perceived the pulses, but it is difficult to connect the increases of ethanol consumption with such perception because of the absence of effect on sucrose consumption.

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DRUG-RFR
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Seaman, R.L. and H. Wachtel
SLOW AND RAPID RESPONSES TO CW AND PULSED MICROWAVE RADIATION BY
INDIVIDUAL APLYSIA PACEMAKERS
J. Microwave Power, Vol. 13, No. 1, pp. 77-86 (1978)

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AUTHOR ABSTRACT: Specific absorption rates (SARs) of microwave energy
that altered firing rates were determined for individual pacemaker
neurons in the abdominal ganglion of Aplysia californica. A stripline
apparatus provided both for artifact-free recording of transmembrane
potentials and for precise determination of the rate of absorption of
microwave energy.

Exposure for two to three minutes at an SAR of only a few mW/g was
capable of changing the firing rate of some pacemakers. Two types of
responses were observed. The response that was seen in all neurons
developed slowly, reaching a steady state in one to three minutes. The
other response was seen in a few neurons and occurred within five
seconds from the onset of irradiation. Similar responses were obtained
for two microwave frequencies, 1.5 and 2.45 GHz. Pulsed radiation
induced rapid changes of firing rate more readily than did CW radiation
at the same SAR.

A convective heating scheme was used to study the effects of temperature
changes on the pacemakers' firing rates. Since all of the responses are
not readily explained by general heating of the preparation, alternate
mechanisms are suggested for the observed effects.

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Study Type: Cellular and Subcellular Effects, Nervous System,
Biorhythms; IN VITRO; APLYSIA
Effect Type: Changes in firing patterns of individual Aplysia pacemaker
and bursting neurons induced by CW and pulsed RFR
Frequency: 1.5 and 2.45 GHz
Modulation: CW; 0.5- to 10-microsecond pulses at 1000 to 5000 pps
Power Density: Not determined
SAR: 0-291 W/kg

EXPOSURE CONDITIONS: After removal from an Aplysia, each abdominal
ganglion studied was placed in artificial seawater at room temperature
(21-26 deg C) within a small acrylic chamber having a wax base. The
ganglion was attached to the center of the base with cactus needles.
The chamber was then inserted in a rectangular stripline transmission
section, between the center conductor and the outer ground conductor.
The stripline section was inserted in a coaxial cable terminated with a
shorted stub. A bidirectional coupler between the source and stripline
section was used to measure forward and reflected average powers. Small
holes in the narrow (ground) walls of the stripline section permitted
transillumination and viewing of the specimen, and insertion of glass

microelectrodes (filled with 2.5 molar KCl) transverse to the electric
field for intracellular recordings. For experiments toward altering
specimen temperatures in the absence of RFR, warm or cold water was
drawn through an enclosed volume surrounding the specimen.

Both CW and pulsed RFR at 1.5 or 2.45 GHz were used. Pulse durations
and repetition rates ranged from 0.5 to 10 microseconds and 1000 to 5000
pps, respectively. Pulse rise times were less than 0.1 microsecond. A
coaxial switch permitted application of the RFR (and removal) within a
few milliseconds. The thermal time constant of the specimen was about 1
min. Exposures were typically for 2-3 min, but were terminated early if
a definite biological response was seen within 1 min.

OTHER INFORMATION: Determination of SARs in such preparations at each
frequency were described in an earlier paper (Wachtel et al., 1975), in
which it was noted that the volume occupied by ganglion and seawater in
different chambers ranged from 0.3 to 0.8 cc. The net power absorbed by
the volume was calculated from the geometry of the stripline, the input
power, and the reflection and attenuation characteristics of the volume.
The results were verified (within a factor of about 2) by measurements
of temperature rises in specimens.

The beating-pacemaker neuron in the abdominal ganglion of Aplysia was
selected for study because it produces action potentials at highly
regular rates with little or no synaptic input and because effects on
single neurons could be studied. Firing rate was measured in terms of
the interspike interval (ISI) recorded on a strip chart along with the
transmembrane potential. After achieving stability in ISI and
transmembrane potential in each preparation, successively higher levels
of RFR were applied for 2-3 min at each level, but the RFR was removed
earlier if the neuron stopped firing.

In the lower range of SARs that yielded effects, firing rates changed
after the onset of the RFR and attained new stable rates with a time
constant of about 1 min. At higher SARs, the changes occurred earlier
during the exposure period. For 46% of the neurons studied, RFR at
sufficiently high SARs consistently reduced the firing rate (100% of
changes). For the other 54%, effective SARs reduced the rate for 79% of
the exposures, but increased the rate for others. For the entire
population of beating-pacemaker neurons, 87% of the responses were
firing-rate reductions. There was no obvious correspondence between the
direction of change and SAR, frequency, or modulation for any single
neuron or for the population in general. For all beating-pacemaker
neurons, post-RFR firing rates returned to pre-RFR rates after 1-2 min.

A representative example was presented in Fig. 1 for a beating-pacemaker
neuron exposed to 1.5-GHz CW RFR at SARs of 5.7, 7.1, and 25.5 W/kg. No
change in peak spike potential was evident at each SAR or with change in
SAR. At 5.7 W/kg, there were also no discernible changes in ISI. At
7.1 W/kg, however, a rise in ISI was evident shortly after the onset of
the RFR; at 7.1 W/kg, the rise was much faster and higher. The authors
noted that the firing-rate decreases of this neuron occurred in 10 of 11

responses to the RFR.

The dose-dependence of the effect on this neuron was presented in Fig. 2 for SARs up to about 69 W/kg. At each SAR, the average firing rate in the interval 10 to 20 seconds after the onset of RFR was normalized to the average for the four action potentials immediately before exposure and the ratio was plotted vs SAR. At low SARs, the normalized firing rates were essentially unity. A least-squares linear-regression fit to the data for the 7 largest SARs was drawn. This procedure was also done for the interval 20 to 30 seconds after RFR onset. For the interval 10-20 seconds, the regression value at 69 W/kg was about 0.6. For the interval 20-30 seconds, the decrease in normalized rate was much steeper: to about 0.5 at 40 W/kg and to 0 at 69 W/kg.

The smallest SARs that produced changes in slow firing rate were determined for 39 neurons from 29 ganglia. The result for the neuron discussed above was 7 W/kg; no other values were given.

In addition to the slow ISI changes, rapid changes were observed in 8 neurons from 8 different ganglia. A rapid change was defined as an increase in firing rate within one ISI of RFR onset, i.e., the ISI occurring either during or just after the onset of RFR was shorter than the pre-RFR ISIs. Within 25 seconds of the firing-rate increase, the rate gradually decreased until it attained nearly the pre-RFR value. The largest rapid change observed was for a neuron that responded uniquely with two separate rate increases when exposed to 0.5-microsecond pulses, 5000 pps, of 1.5-GHz RFR at peak and average SARs of 400 and 1 W/kg. A recording for this neuron, presented in Fig. 3A, showed a step decrease in ISI to a plateau for the first few seconds after RFR onset, at which time a sudden additional ISI decrease occurred, followed by a gradual return toward pre-RFR level. The average SAR, 1 W/kg, was smaller than any of the threshold values for slow firing-rate changes and was the lowest value for all rapid changes as well.

The authors stated: "Rapid changes in firing rate were seen for 2.45 GHz CW and PW and for 1.5 GHz PW. Although the sparse data on this response prevented a systematic analysis, it seemed that the rapid change was better defined for PW than for CW radiation. The rapid changes also tended to occur at smaller averaged SARs for PW radiation." The authors also noted that two neurons exhibited a decrease in firing rate at termination of RFR. A recording was displayed in Fig. 3B for one of these neurons, which exhibited the firing-rate decrease on cessation of 1.5-GHz CW RFR at 8.4 W/kg.

The authors suggested that a possible mechanism for firing-rate changes in beating pacemakers during RFR exposure is the consequent temperature increase of the preparation. This hypothesis was tested by comparing the responses of 29 neurons to heating by RFR and by convection. The temperature time courses and increments were matched. Firing-rate changes with heating (presumably by either method) were slow, requiring 30 to 60 seconds to reach steady state. In this subpopulation of

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neurons, 94% of the changes were reductions in firing rate and 62% of the cells responded similarly to RFR- and convection heating. However, the authors noted that in the preliminary study (Wachtel et al., 1975), "the slow responses of some cells to microwave radiation did not always duplicate those to conventional heating. No rapid changes in firing rate were seen when cells were warmed or cooled by convection."

The authors suggested direct interaction of the RFR with the neurons as another possible mechanism. Shown in Fig. 3C was an example of the firing rates of a neuron during successive intervals of injection of 2, 3, and 2 nA of depolarizing current. The recording shows a higher firing rate during the 3-nA interval than during the preceding and subsequent 2-nA intervals. There was no significant change in spike amplitude. The authors stated: "These rapid changes, each of which adapts to an intermediate value, resemble those seen at the onset and termination of irradiations. Microwave radiation produced the same effect as an increase in depolarizing current."

The other type of neuron selected for study was the bursting-pacemaker cell in the abdominal ganglion of Aplysia. These neurons produce action potentials in bursts coincident with an endogenous, depolarizing slow-wave potential. Their otherwise highly regular interburst intervals (IBIs) can be modulated by synaptic input from other neurons in the ganglion. Only bursting pacemakers without synaptic potentials were studied, to help insure that observed effects were occurring in single neurons. Also, bursting pacemakers were required to exhibit regular IBIs, either spontaneously or on injection of a small depolarizing current, criteria that were met by about 20% of the neurons tested. Bursting and beating pacemakers were often studied in the same ganglion.

The exposure procedure used was similar to that for beating pacemakers, and smallest effective SARs were determined. Representative responses of a bursting pacemaker to 7.3, 16.0 and 21.6 W/kg were displayed in Fig. 4, a low-resolution reproduction that displayed bursts as thick spikes. At each level, there were minor variations (increases and decreases) of IBI apparently not associated with the RFR. Exposure at 7.3 W/kg (Fig. 4A) had no apparent effect; there were no clear RFR-induced differences in IBIs, which ranged from 10.4 to 12.3 seconds during the entire pre-RFR and exposure time interval shown in Fig. 4 (about 2 min). At 16.0 W/kg (Fig. 4B), however, the bursts were of longer duration (thicker) than those before exposure (which were comparable to those at 7.3 W/kg), and the mean IBI after onset of RFR was smaller than before onset. The pre-RFR range of IBIs was 8.2 to 8.7 seconds, but the range during exposure was difficult to discern from the figure because of the longer durations of the bursts. At 21.6 W/kg (Fig. 4C), the burst durations before and during exposure were similar to those at 7.3 W/kg; however, the pre-RFR IBIs ranged from 11.0 to 12.1 seconds, whereas the range during exposure was 7.2 to 11.2 seconds, a clear reduction of mean IBI.

The smallest effective SARs were determined for 16 bursting pacemakers from 12 ganglia. The authors noted that the post-RFR IBI did not always

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return to the pre-RFR value after 2-3 min of exposure. They also
indicated that all these pacemakers exhibited a slow, graded response
(exemplified in Fig. 4), but that the direction of change was not the
same for all cells; 7 cells showed decreased IBIs, 3 cells showed
increased IBIs, and the IBIs of the other 6 showed changes in both
directions. For cells exhibiting increased IBIs, the cells would stop
firing at sufficient SAR and duration, as evidenced by steady
hyperpolarized membrane potentials. The authors noted that, as in the
previous study (Wachtel et al., 1975), responses of a given cell to
convective warming were not always in the same direction as the RFR
responses of that cell, again suggesting more than a simple heating
effect.

Some bursting pacemakers exhibited phasic responses at the onset or
termination of RFR. For 3 cells that yielded a smaller IBI-steady-state
response to RFR, the IBI at the onset of RFR was longer than the IBI
just before or after, a response that was seen occasionally with
convection heating. For 2 cells, the IBI at RFR termination was shorter
than the IBIs immediately preceding and following termination, a
response that was not seen with convection cooling. Phasic responses
occurred during exposure to 1.5- and 2.45-GHz CW RFR at SARs from 7 to
291 W/kg.

The authors indicated that the IBIs of bursting pacemakers were also
sensitive to injected currents: "The change in IBI as a result of an
increase in injected hyperpolarizing current resembled the phasic
increase of IBI that occurred at the onset of irradiation. Also, a
decrease in hyperpolarizing current caused a phasic decrease of IBI
similar to that which occurred at the termination of irradiation. Thus,
microwave energy seemed to act in the same way as an injected
hyperpolarizing current."

The results for the 39 beating-pacemaker and 16 bursting-pacemaker
neurons were summarized in Fig. 5 in the form of histograms of the
frequency distributions of the smallest SARs that caused slow changes in
firing patterns. The authors merged the data for CW and pulsed RFR at
both RFR frequencies, since no difference in effectiveness was seen
among them. The combined histogram for both kinds of neurons showed a
rough resemblance to a normal distribution. These histogram values were
then plotted in Fig. 6 as the percentage of neurons that responded at a
given or smaller SAR (cumulative percent responses) on a probability
scale vs the smallest effective SARs on a logarithmic scale. The data
fitted a straight line with only small deviations. The lower and upper
ends of the line showed that 1% of the 55 neurons responded to about 2
W/kg and 99% of the neurons responded to about 100 W/kg; the median SAR
(50%) was 14.5 W/kg. The authors stated: "The proximity of the data
points to a straight line indicated that the distribution of smallest
effective SARs can be represented by a log-normal distribution."

The authors noted that spontaneous firing rates of nonpacemaker neurons
in the abdominal ganglion were affected (increased slightly) only for
SARS greater than about 50 W/kg, whereas over 90% of the pacemaker

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neurons were affected at this SAR, an indication of the higher
sensitivity of pacemaker neurons to RFR.

CRITIQUE: The authors suggested that the slow responses of pacemakers
to RFR were largely thermally induced, because the responses followed
time courses similar to specimen-temperature rises and depended on the
average SAR (with a thermal sensitivity of 0.02 deg C per W/kg) and not
on modulation or frequency. However, they stated: "On the other hand,
that a slow response was not always duplicated by identical irradiations
and that irradiation did not always elicit the same response that was
elicited by thermal stimulation weaken the argument for a purely thermal
interaction." This point is open to question, because unlike convective
heating, in which heat is transferred into the specimen-seawater volume
via the surface of the volume, internal heating would occur from
significant RFR penetration into the volume at the two frequencies used.
Thus, similar heating patterns by the two modes would not be expected.
Moreover, although presumably the ambient temperature remained basically
constant during each RFR exposure, it is not clear that the ambient
temperature (ranging from 21 to 26 deg C) was the same for all RFR
exposures (during which no convective fluid was used).

The authors also stated: "The rapid changes seen in beating pacemakers
and some of the phasic responses seen in bursting pacemakers cannot be
readily attributed to a thermal mechanism. These responses took place
much faster than the increase in temperature of the preparation. This
was more obvious for beating pacemakers, probably because the ISI
provided finer resolution of time than did the IBI. Both the rapid and
phasic changes were in a direction opposite to the majority of slow
changes, which followed temperature. In addition, no rapid responses
were observed when temperature was similarly increased by convective
means. One mechanism that could explain the rapid changes is a direct
action of the electromagnetic field on the neuron... There also exists
the possibility that the pacemakers were sensitive in some way to the
mechanical energy created by the absorbed microwave energy...In our
study, rapid on- and off-incident energy occurred during PW radiation
and for the onsets and terminations of irradiations, all being
occurrences for which rapid changes seemed to be enhanced. However, it
still remains to be determined whether pacemakers of Aplysia can detect
small shock waves." These points were logical, but require experimental
verification.

Also considered was that the rapid responses resulted from RFR-induced
currents in the neuron. However, they noted that their experimental
results were in conflict with this hypothesis: "In their rapid
responses, beating pacemakers always responded as if to a depolarizing
current; the bursting pacemakers, always as if to a hyperpolarizing
current. We cannot easily explain these opposite effects in terms of
induced currents since we would expect that induced current would flow
in one direction (equivalent DC) so that the responses of all cells
would mimic the responses to one polarity of injected current."

Perhaps insufficiently considered were the variations in responses among

specimens due to uncontrolled non-RFR factors and those by individual specimens at various times. Exemplifying the latter point were the results for the bursting pacemaker exposed at 7.3, 16.0, and 21.6 W/kg (see the previous section); the pre-RFR IBIs for the intermediate SAR (range 8.2-8.7 seconds) were much shorter than the IBIs for 7.3 W/kg (range 10.4-12.3 seconds) and the pre-RFR IBIs for 21.6 W/kg (11.0-12.1 seconds).

In tests by the authors, use of glass microelectrodes filled with 2.5-M KCl yielded less than 0.01 nA on RFR exposure, lower than that required to cause measurable changes in pacemaker firing rates. Nevertheless, possible electrode artifact may not be ruled out entirely, because Yee et al. (1984) showed that 3-M KCl electrodes yielded artifactual responses in the beating rate of the isolated frog heart during exposure to 2.45-GHz RFR at 8.55 W/kg

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Bioelectromagnetics, Vol. 5, No. 2, pp. 263-270 (1984)

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SEAMAN
WACHTEL

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APLYSIA
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Peterson, D.J., L.M. Partlow, and O.P. Gandhi
AN INVESTIGATION OF THE THERMAL AND ATHERMAL EFFECTS OF MICROWAVE
IRRADIATION ON ERYTHROCYTES

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AUTHOR ABSTRACT: Erythrocytes heated by either microwave irradiation or
conventional techniques were examined for loss of hemoglobin (Hb) and
potassium (K+). In all experiments, microwave heated red blood cells
(RBC´s) were directly compared with RBC´s warmed to the same temperature
by use of an adjustable incubator and with RBC´s maintained at room
temperature. Microwave irradiation was carried out at either 2.45 GHz
or in selected 0.5 GHz swept frequency regions in the 12.5-18 GHz range.
Sample temperature was continuously monitored in both microwave heated
and conventionally heated samples by use of a relatively nonperturbing
liquid crystal optic fiber temperature probe.

When rabbit RBC´s were warmed by 3.7 deg C for 45 min by either
irradiation (2.45 GHz, 10 mW/sq cm) or conventional heating, no
additional Hb or K+ was released into the supernatant. In contrast,
when rabbit RBC´s were rapidly warmed from room temperature to 37 deg C
by either technique, the heated erythrocytes lost significantly more of
both Hb and K+ than equivalent RBC´s maintained at room temperature. In
addition, RBC´s warmed to 41.5 deg C by either technique lost far more
Hb and K+ than those warmed to 37 deg C.

In all experiments, Hb and K+ were lost in equal amounts by microwave
heated and conventionally heated erythrocytes warmed at the same rate to
the same final temperature. Thus, at all frequencies and power levels
tested, any increased loss of either Hb or K+ from microwave irradiated
rabbit RBC´s should be ascribed to thermal effects on the stability
and/or permeability of the erythrocyte membrane.

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Study Type: Cellular and Subcellular Effects, Immunology and
Hematology, Physiology and Biochemistry; IN VITRO; RABBIT, HUMAN
Effect Type: RFR-induced leakages of hemoglobin and potassium ions out
of rabbit and human erythrocytes
Frequency: 2.45 GHz; Ku bands 12.5-13, 13.5-14, 14.5-15, 15.5-16,
16.5-17, and 17.5-18 GHz
Modulation: CW at 2.45 GHz; each band swept (FMCW) at unspecified rate
Power Density: 10-140 mW/sq cm at 2.45 GHz; 31-124 mW/sq cm in Ku bands
SAR: 4.6 W/kg per mW/sq cm at 2.45 GHz; not indicated for Ku bands

EXPOSURE CONDITIONS: Suspensions of rabbit or adult-male-human blood in
veronal-buffered saline solution containing gelatin were centrifuged to
pellet the red blood cells (RBCs), and the pellets were resuspended in
a similar solution. Aliquots of each suspension were placed in 0.4-ml
polypropylene microcentrifuge tubes with caps and were exposed to RFR in

one of two systems or conventionally heated or maintained at room
temperature as controls.

Exposures to 2.45 GHz were done in system I. Samples were placed in the
far field of a horizontally radiating horn (137 cm from an aperture
34.5 x 49.5 cm) powered by a magnetron. In the first experiment, 4
samples were inserted parallel to one another in equally spaced slots
along one edge of a rectangular Styrofoam block and 3 along the opposite
edge. Exposures were done with the block vertical and stationary, and
with the long axes of the tubes parallel to the E vector. The holder
used for subsequent 2.45-GHz experiments was a Styrofoam disc, into
which 8 samples were inserted radially at equal angular spacing. The
disc was mounted vertically (axis horizontal) on a motor with a long
Teflon shaft and rotated at 2 rpm. The motor was shielded with RFR-
absorption material.

In system II, a horizontally radiating horn (aperture 2.0 x 2.5 cm)
powered by a sweep oscillator was used for exposures to each band
selected within the Ku region 12.5 to 18 GHz. The sample holder used
was the rotating disc described above, which was placed 10 cm from the
horn aperture (far field).

OTHER INFORMATION: Incident power densities at 2.45 GHz were measured
with a Narda 8110B radiation monitor. Due to unavailability of suitable
instruments for the Ku region, incident power densities in this region
were calculated from the transmitted power, wavelength, dimensions of
the horn aperture, and distance to the sample holder.

SARs were determined from measurements of temperature rises in samples
exposed to high levels of RFR for short intervals (to minimize errors
due to heat losses). As noted later, the normalized SAR for 2.45 GHz
was 4.58 W/kg per mW/sq cm. However, no explicit SAR data were given
for the Ku region.

In the experiment with the stationary rectangular sample holder, 7
sample tubes containing rabbit RBCs, comprising a microwave-heating
(MWH) group, were heated from 22 deg C (room temperature) to 37 deg C
with 2.45-GHz RFR in about 15 min, after which the temperature was held
constant for 30 min (which required an average power density of 35 mW/sq
cm to maintain). To measure specimen temperatures, exposures were
interrupted briefly every 10 min for insertion of a thermocouple. For
comparison, 7 samples of rabbit RBCs, comprising a conventional-heating
(CH) group, were heated along approximately the same temperature-vs-time
profile in a water bath. Another group of 7 rabbit-RBC samples was held
at 22 deg C (a room-temperature or RT group).

After such treatments, the samples were centrifuged and the supernatants
were removed and stored in other microcentrifuge tubes. Hemoglobin (Hb)
and potassium-ion (K+) concentrations in the supernatants were measured
with a spectrophotometer and a flame-photometer, respectively. The
results were normalized to the values obtained from untreated samples

ruptured by sonification and similarly assayed, and were compared for statistical significance with Student's t-test at the 0.02 level.

The mean normalized values (in percent) were displayed as bar graphs with SEM bars. The mean percentage of hemolysis for the CH group was slightly but significantly higher than for the RT group. (The values for both were less than 1%, with SEMs of about 0.08). By contrast, the mean for the MWH group was about 3.5% (+/- 0.9) which, despite the more than tenfold larger SEM, was significantly higher than for either of the other groups. The mean K+ release by the RT group was about 5% (SEM too small to discern). The K+ values for the CH and MWH groups were about 17% (+/- 1.2) and 37 (+/- 8.4), respectively, which significantly differed from one another and from the value for the RT group.

The much larger SEMs for the MWH group led the authors to surmise that the apparent RFR-induced enhancement of Hb and K+ losses obtained with the stationary holder were incorrect and misleading because of large spatial variations of SAR. They then determined the SARs of the RBCs at the 7 sample positions, using a power density of 43 mW/sq cm for 1 min, which yielded values ranging from 174.3 to 348.9 W/kg (at locations 3 and 5 on opposite sides of the holder). Moreover, the losses from the samples exposed at the higher SARs were larger than the losses from the other samples. Therefore, the rotating specimen holder, which provided the added advantage of continual mixing of each sample, was used in all subsequent experiments. In addition, a nonperturbing liquid-crystal, optic-fiber (LCOF) probe was used to continuously monitor the temperature of one of the samples during exposure.

Measurements of SARs in the rotating holder at 2.45 GHz with 43 mW/sq cm for 2 min yielded only minor variations (195.3 W/kg at diametrically opposite locations 2 and 6; 198.8 W/kg at diametrically opposite locations 4 and 8). Thus, the normalized mean SAR was 4.58 W/kg per mW/sq cm. Vertical rotating sample holders were also used for the comparison CH groups (which were heated in a hot-air incubator instead of a water bath) and RT groups.

In the next experiment, an MWH group of samples of rabbit RBCs was exposed to 2.45-GHz RFR at 10 mW/sq cm (45.8 W/kg) for 45 min, which resulted in a steady rise from 25.0 deg C to a final temperature of 28.7 deg C. A CH group was subjected to the same temperature profile, and an RT group was held at 25.0 deg C. The bar graphs for hemolysis and K+ release showed no significant differences among the three groups for either endpoint; hemolysis was about 0.4% and K+ release was about 6%.

In a similar experiment, an MWH group was heated from 23 to 37 deg C in about 8 min by exposure at 86 mW/sq cm (394 W/kg) and held at the latter temperature by exposure at 35 mW/sq cm (160 W/kg) for the remaining 37 min; CH and RT groups were used for comparison as before. The results showed no significant differences between the MWH and CH groups for hemolysis (both about 0.5%) or K+ release (about 9%), but the values for both groups were significantly larger than for the RT group (hemolysis about 0.3%, K+ release about 7%).

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oups of samples of rabbit RBCs were also heated from room temperature
1-24 deg C) to 37 deg C by exposure to each of the 0.5-GHz-wide swept-
equency bands in the Ku region at 124 mW/sq cm, and were held at 37
g C by exposure at 31 mW/sq cm. Again, CH and RT groups were used for
mparison. For each band (Fig. 7 of the paper), the differences
tween the MWH and CH groups for each endpoint were not significant and
e means for both groups were significantly larger than for the RT
oup. Figure 7 also showed apparently significant interband
fferences among the various MWH groups for each endpoint, but these
fferences probably were not RFR-related because similar interband
fferences were evident for the CH and RT groups.

e authors indicated that many replications of the experiments with
abbit RBCs warmed to 37 deg C by exposure to 2.45 GHz and the band
7.5-18 GHz had been performed, and they tabulated the results for 3
eplications with 2.45 GHz and 5 replications with 17.5-18 GHz. For
ach such experiment, the mean values of both endpoints for the MWH and
H groups were significantly larger than for the RT group, but did not
iffer significantly from one another. There were significant
ifferences in hemolysis among the 5 MWH groups exposed to 17.5-18 GHz
ranging from 0.6% +/- 0.06 to 2.1% +/- 0.12), but similar differences
ere obtained for the corresponding CH groups (range 0.6% +/- 0.06 to
.2% +/- 0.08) and the RT groups (range 0.3% +/- 0.03 to 1.6% +/- 0.04),
ndicating again that these differences were not RFR-related. Similar
emolysis findings were obtained for the 3 groups exposed to 2.45 GHz.
he results for K+ release exhibited the same behavior as for hemolysis.

roups of samples of human RBCs were heated to 37 deg C by exposure to
.45 GHz at 90 mW/sq cm (412 W/kg) for about 8 min and held there for 37
in by exposure at 30 mW/sq cm (137 W/kg). Unlike those for rabbit
BCs, the results showed no significant differences among the MWH, CH,
nd RT groups in either hemolysis (about 0.6%) or K+ release (about 6%).

abbit RBCs were heated to 37 deg C in about 4 min or twice the previous
ate by RFR exposure (presumably 2.45 GHz) at 140 mW/sq cm (641 W/kg)
nd held there for the remaining 41 min by exposure at 34 mW/sq cm (156
/kg). Other samples were heated to 37 deg C in about 16 min (half the
revious rate) by exposure at 43 mW/sq cm (197 W/kg) and held there with
4 mW/sq cm (156 W/kg). The results of each experiment were consonant
ith those of the similar previous experiments, i.e., there were no
ignificant differences between the MWH and CH groups in either
ndpoint, and the values for both groups were significantly higher than
or the RT group in each case. Comparison of the values for the two
eating rates indicated apparently slightly larger hemolysis for the
aster than the slower group and the converse for K+ release, but again
imilar behavior occurred for the RT groups.

abbit RBCs were heated to 41.5 deg C in about 13 min with 2.45-GHz RFR
t 112 mW/sq cm (513 W/kg) and kept at that temperature for 32 min with
3 mW/sq cm (426 W/kg). Once again, there were no significant
ifferences in values between MWH and CH groups, but the results for
emolysis and K+ release for these groups were about 22 and 7 times

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CRITIQUE: The experimental results of this carefully performed study are unequivocal. However, the phase-transition region (17.7-19.5 deg C) for the RFR-exposed RBCs is not as clearly delineated as implied by the authors. As noted above, relatively small but statistically significant increases of RFR-induced Na-22 influx were evident at temperatures outside the stated transition region, i.e., at 16.5 and 21.5 deg C. The latter data may indicate merely that the transition region is larger. It is also interesting that the influx data in Fig. 1 for the RFR-exposed RBCs over the region from 17.7 to 23 deg C (which includes the transition) showed a small increase with decreasing temperature, i.e., that the slope was slightly positive over the region. Perhaps purely coincidental, the occurrence of a positive slope is qualitatively similar to the "zigzag" observed by Olcerst et al. (1980) in the transition region of sham-exposed RBCs, noted by the authors as absent in their study.

Peterson et al. (1979) and Liu et al. (1979) reported obtaining equal increases of K+ efflux for rabbit RBCs heated from room temperature to 37 deg C by conventional means or by exposure to 2.45-GHz RFR at relatively high SARs, e.g., 394 W/kg (86 mW/sq cm) (Peterson et al., 1979). Also reported was increased hemolysis. Similar results were also obtained by Hamrick and Zinkl (1975). The results of all three of these studies were at variance with those of Baranski et al. (1971, 1974) and Ismailov (1971), who reported increased K+ efflux from rabbit RBCs exposed to 1- or 3-GHz RFR at power densities as low as 1 mW/sq cm. However, none of these investigators conducted experiments with samples held at constant temperature during exposure, which might have revealed the existence of phase transitions.

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Radio Sci., Vol. 14, No. 6S, pp. 109-115 (1979)

influx of RBCs exposed to RFR at temperatures outside the transition region.

The silver-staining assays of supernatants after RFR- and sham-exposure were displayed in Fig. 3 for pO2 values of 5, 150, and 760 mmHg. The results indicated the shedding of proteins with molecular weights in the approximate range 8,000-28,000 D. Proteins at 26,000 and 24,000 D were visible only in the supernatants from RFR-exposed RBCs. A protein at 28,000 D was visible for both RFR- and sham-exposed samples, but was more prominent for RFR-exposed RBCs. This was also true for proteins at 15,000, 14,400, 13,000, 11,000, 10,000, and 8,000 D. By contrast, proteins at 20,000 and 18,000 D shed by sham-exposed RBCs were more prominent than those shed by RFR-exposed RBCs. Protein release was not detected for RBCs exposed to RFR at temperatures outside the transition region (no assays presented).

The authors observed that since equal amounts of protein standard (20 micrograms) were used for each assay, the results suggest the occurrence of differential release of at least 11 proteins. They estimated that the upper limit of protein-release detectability was 450 femtograms per rabbit erythrocyte, which corresponds to about 1% of the total protein mass (membrane and cytosolic) found in the human erythrocyte, and indicated that this silver-staining technique was about a hundredfold more sensitive than the standard Coomassie-blue staining technique.

Citing appropriate references, the authors stated: "The bands we observe are distinct from major erythrocyte membrane proteins, with the possible exception of the band at MW 28,000 D which may represent band 7 protein. Since a specific channel and an associated carrier protein responsible for Na transport have not been identified, it is not possible to relate the release of proteins to the increase in Na-22 influx that we observe. It is notable, however, that protein shedding is most pronounced at pO2 values of 5 and 760 mm Hg, where Na-22 influx is also most pronounced (Fig. 2)."

In their discussion, the authors reiterated the care taken to ensure that temperatures during RFR exposure were held constant to within +/- 0.05 deg C throughout the sample, and stated: "This effectively rules out gross thermal effects as being involved in the permeability changes we observe, but leaves open the possibility of microheating of the cell membrane itself." They also noted that specific mechanisms responsible for the pO2 dependence of Na-22 influx in the transition region are speculative at present. They mentioned that RFR- and sham-exposed erythrocytes were intact and appeared to be morphologically normal under examination by light microscopy, thus indicating the absence of gross membrane disruption and suggesting that the proteins released were most likely the peripheral or extrinsic proteins associated with the membrane surface. As an alternative hypothesis, they suggested the possibility that the proteins detected were intracellular and had leaked out during RFR- or sham-exposure, and noted that they had detected some hemoglobin (the 14,400-D band) in the cell-free supernatants of all samples.

regions above 19.5 and below 17.7 deg C, the activation energies were
6.5 and 14 kcal/mole, respectively. This change is indicative of a
protein-lipid or lipid-lipid phase transition. The broad phase
transition is characteristic of natural membranes and is unlike the
sharp transitions (0.1-0.2 deg C) for two-component phospholipid
bilayers.

For the RBCs exposed to RFR, the authors stated that increases in Na-22
influx of 75-100% (relative to the influx for sham-exposed RBCs)
occurred only in the 17.7-19.5 deg C transition region. These
increases were evident in Fig. 1. However, Fig. 1 also showed small
(10-15%) but apparently statistically significant increases at about
16.5 and 21.5 deg C. At 17.7 deg C, the increase was about 100%.
Extrapolation of the linear region above 19.5 deg C toward higher
temperatures indicated that a temperature increase of about 10 deg C (to
about 27.7 deg C) would be necessary to achieve the same increase of Na-
22 influx in sham-exposed RBCs as in RBCs exposed to RFR while held at
17.7 deg C.

The authors noted that Olcerst et al. (1980) had reported an increase of
permeability to Na-22 of rabbit RBCs exposed to 2.45-GHz CW RFR at SARs
exceeding 60 W/kg while held at 22.5 deg C, where the Arrhenius plot
showed an unusual vertical "zigzag" [a transition region of positive
slope]. Liburdy and Penn stated: "The latter indicates that a phase
transition was not operative; such a feature has not been previously
reported in the literature and is not readily interpretable. We have
been unable to reproduce these findings using the same procedures and
apparatus employed by Olcerst." The authors indicated that in the
present study, RBCs were continually maintained in suspension to avoid
settling and the formation of thermal hot spots, and that sample
temperatures were measured directly during RFR exposures rather than
estimated from measurements of differential dodecane temperatures as was
done by Olcerst et al. (1980).

The authors also noted that prior studies of the effects of in-vitro
exposure of erythrocytes to RFR were done at atmospheric pO2 (150 mm
Hg), which is far from in-vivo intracellular values in tissue (<30
mm Hg). Therefore, they varied pO2 from 0 to 760 mmHg by gently
bubbling each desired premixture of O2 and N2 through samples. A
typical plot of Na-22 influx in sham-exposed RBCs held at 17.7 deg C for
30 min vs pO2, presented in Fig. 2, showed about the same mean influx
as obtained previously, with no significant dependence on pO2. For RFR-
exposed RBCs, however, Na-influx was significantly higher at all pO2
values than for sham-exposed RBCs. Specifically, at intracellular pO2
(0-5 mm Hg), the influx was almost 3 times higher than the value for the
sham-exposed RBCs; at venous pO2 (35 mm Hg), the influx decreased but
was more than twice that of the sham-exposed RBCs; at arterial and
atmospheric pO2 values (90 and 150 mm Hg, respectively), the influx
values both decreased slightly to less than twice that of the sham-
exposed RBCs; and at hyperoxic pO2 (760 mm Hg), influx increased to
about 2.5 times that of the sham-exposed RBCs. In addition, the authors
noted without presenting data that changes of pO2 did not alter Na-22

temperature rise measured in a nonthermostatted sample. For 60 W/kg, the rate was 0.86 deg C/min. Control samples were sham-exposed in the same apparatus. In all experiments, a stream of premixed O2/N2 was gently bubbled into the sample compartment to maintain erythrocytes in suspension and to control oxygen tension. This feature also eliminated thermal gradients larger than +/- 0.05 deg C in the sample, as measured with the Vitek probe.

OTHER INFORMATION: Red blood cells (RBCs) for each experiment were obtained from 1 of 4 adult male New Zealand rabbits bled at staggered 30-day intervals. The RBCs were washed three times with buffered Ringer's solution at 4 deg C, with care taken to remove all leukocytes. For assay of Na-22 uptake, a 1.4-ml sample of RBCs was pretreated with 0.1 mM of ouabain for 90 min at 37 deg C (to inhibit the membrane Na+/K+ pump) and was inserted in the sample compartment. Direct pO2 measurements with a thermostatted Clark oxygen electrode were made before and after RFR exposure. Intracellular (0-5 mm Hg), venous (35 mm Hg), arterial (90 mm Hg), atmospheric (150 mm Hg), and hyperoxic (760 mm Hg) conditions were simulated. RBCs were equilibrated at pO2 values for 20 min prior to onset of Na-22 influx measurements.

Immediately before RFR- or sham-exposure, 4 microcuries/ml of Na-22 were added. After 10, 20, or 30 min of exposure, the RBCs were washed three times again at 4 deg C. Na-22 uptake was assayed by scintillation counting of gamma emissions and was found to be linear with time for both RFR- and sham-exposed samples.

Hemolysis was assessed by use of the cyanmethemoglobin method to determine the amount of hemoglobin present in the cell-free supernatant. Hemolysis increased slightly with temperature; a maximum of 2% of intracellular hemoglobin was released at 25 deg C. However, there were no differences in hemolysis between temperature-matched RFR- and sham-exposed samples.

Immediately after RFR- or sham-exposure, samples were centrifuged, and protein content of the cell-free supernatants was determined. Electrophoresis on 12.5% acrylamide slabs in the presence of sodium dodecyl sulfate (SDS) was followed by silver staining. Each well was loaded with 0.02 mg of protein that included 0.001 mg of bovine serum albumin (BSA) in the supernatant to serve as an internal standard. Slabs were silver-stained for 10 min and developed for 15 min. The markers used were lysozyme (14,400 D), carbonic anhydrase (31,000 D) ovalbumin (45,000 D), BSA (68,000 D), and phosphorylase B (92,000 D).

The temperature dependence of Na-22 influx for 30 min of RFR- or sham-exposure of RBCs was displayed in Fig. 1. The Arrhenius plot (log of Na-22 influx per hr per gram of RBCs vs the inverse of the absolute temperature) for the sham-exposed RBCs over the temperature range from about 15 to 25 deg C showed two linear regions of negative slope, with a nonlinear transition region between 17.7 and 19.5 deg C. The transition is consistent with nonlinear regions in the range 18-20 deg C for RBCs from a variety of sources. From the negative slopes for the linear

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Liburdy, R.P. and A. Penn
MICROWAVE BIOEFFECTS IN THE ERYTHROCYTE ARE TEMPERATURE AND pO2
DEPENDENT: CATION PERMEABILITY AND PROTEIN SHEDDING OCCUR AT THE
MEMBRANE PHASE TRANSITION
Bioelectromagnetics, Vol. 5, No. 2, pp. 283-291 (1984)

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AUTHOR ABSTRACT: Microwave exposure (2450 MHz, 60 mW/g, CW) of rabbit
erythrocytes increases Na passive transport only at membrane phase
transition temperatures (Tc) of 17-19 deg C. This permeability effect
is enhanced for relative hypoxia which is characteristic of
intracellular oxygen tension (pO2 less than or equal to 5 mm Hg).
Neither the permeability nor the pO2 effects are observed in
temperature-matched (+/- 0.05 deg C), sham-exposed controls. In
addition, at Tc, microwave exposure is observed to induce the shedding
or release of two erythrocyte proteins not seen in sham-exposed
controls. Moreover, the enhanced shedding of at least seven other
proteins all of molecular weight less than or equal to 28,000 D was
detected in the microwave-treated samples. Using sensitive silver
staining we estimate that approximately 450 fg of protein were shed per
erythrocyte. These results demonstrate that temperature and pO2 are
important influences on both functional and structural responses of cell
membranes to microwave radiation.

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Study Type: Cellular and Subcellular Effects, Mechanisms of
Interaction, Immunology and Hematology, Physiology and Biochemistry;
IN VITRO; RABBIT
Effect Type: Increases of sodium-ion influx for rabbit erythrocytes
exposed to RFR at membrane transition temperatures, and enhancement of
the effect under relative hypoxia and hyperoxia
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not indicated
SAR: 60 W/kg

EXPOSURE CONDITIONS: Exposures of erythrocyte suspensions were done in
a system similar to that described by Rabinowitz et al. (1977). The
exposure cell consisted of two concentric Teflon compartments. The
inner compartment (ID 0.6 cm, length 3 cm) was designed to hold about 1
ml of suspension. The temperature of the sample was held constant at
any desired value to within +/- 0.05 deg C by flowing thermostatically
controlled dodecane through the outer compartment. (Both Teflon and
dodecane are virtually transparent to 2.45-GHz RFR.) The exposure cell
was inserted transversely into the center of a section of WR-430
rectangular waveguide along the direction of maximum electric field (for
the TE10 mode). Forward and reflected powers were measured continuously
and a nonperturbing Vitek thermistor probe was used to monitor sample
temperature during exposure. The SAR was determined from the rate of

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OLCERST
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rabbit erythrocytes (unpublished). They then stated: "Because we have not observed increases in efflux for passive ionic efflux or the efflux of 3-0-methylglucopyranoside along the linear regions of the Arrhenius plot, the hypothesis of a leaky membrane can be discounted."

However, the phrase "macroscopic thermal mechanism" in item (b) is obscure. Coexistence of two phases in a phase transition implies the requirement for absorption or release of latent energy (i.e., without temperature change) to complete a transformation from either phase to the other, and the interaction mechanism in the present study is not readily characterized.

The results of this study are not fully consistent with those of Liu et al. (1979) and Peterson et al. (1979), who reported not only increases of K+ efflux but also hemolysis (the latter effect absent in the present study, but not commented on by the authors) for rabbit erythrocytes heated from room temperature to 37 deg C by either conventional means or by RFR exposure at SARs in the range 46-641 W/kg, thus indicating that the effects were thermally induced. However, in the present study, differences in efflux between RFR-exposed and control specimens were made at substantially constant temperature, i.e., most of the heat generated by the RFR was removed by the dodecane coolant during exposure, whereas the efflux differences determined by Liu et al. (1979) and Peterson et al. (1979) were for relatively large temperature changes. Thus, perhaps comparisons of the findings of the present study with those of the latter two are not warranted.

In a subsequent study, Liburdy and Penn (1984) reported the occurrence of increased sodium passive transport at a membrane phase transition temperature within 17-19 deg C for rabbit RBCs exposed to 2.45-GHz RFR at 60 W/kg. They indicated that maximum effect occurred for hypoxia and hyperoxia (relative to atmospheric p02), produced by bubbling appropriate 02/N2 mixtures through samples, a parameter not controlled by previous investigators. They noted that with the same apparatus and procedures used by Olcerst et al. (1980) but with better control and measurement of sample temperature (to +/- 0.05 deg C), they were unable to reproduce the regions of positive slope found by the latter for control RBCs. Though not apparently recognized by Liburdy and Penn, however, their data for RFR-exposed RBCs appears to indicate a small but analogous positive-slope region.

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DEPENDENT: CATION PERMEABILITY AND PROTEIN SHEDDING OCCUR AT THE
MEMBRANE PHASE TRANSITION
Bioelectromagnetics, Vol. 5, No. 2, pp. 283-291 (1984)

between regions 2 and 3, it was -37.56; and for the transition (35.5-36 deg C) between regions 3 and 4, it was -116.67. From Table I, at a mean temperature of 22.5 deg C, the ratio was 1.64 (0.91) at 100 W/kg, 3.80 (0.47) at 190 W/kg, and 1.73 (0.79) at 390 W/kg, again nonmonotonic with SAR. At 13.0 deg C, the ratio was 7.66 (8.71) for 390 W/kg; at 35.5 deg C, it was 1.45 (0.38) for 190 W/kg; and at 36.0 deg C, it was 2.42 (0.59) for 190 W/kg. (Again, values for other SARs were not given.)

The authors summarized the results as follows:

"(a) Microwaves increase the passive transport of both sodium and rubidium from rabbit erythrocytes only at temperatures where the Arrhenius plot is not linear.

(b) The experimental conditions of these studies permitted control of the sample temperature to a degree that would preclude an explanation of this increase by a macroscopic thermal mechanism.

(c) The data suggest that existence of an intermediate configuration within the membrane is necessary for the observation of increased efflux. This could be either the simultaneous existence of two phases or an intermediate protein configuration.

(d) The efflux response does not increase monotonically with increased absorbed power."

CRITIQUE: Item (a) of their summary appears to be supported by the data in their Figs. 3 and 4. RFR-induced efflux increases were obtained only in the transition (positive-slope) regions; within the negative-slope regions, the effluxes of Na and Rb with RFR were essentially the same as control values at corresponding temperatures. However, there is a peculiar ambiguity in both figures: for almost all of the RFR points in the negative-slope regions (those represented by filled diamonds), the SAR value was not stated. (Filled circles, squares, and triangles were used to indicate 100, 190, and 390 W/kg, respectively.) It might have been more illuminating if efflux values vs SAR for the nontransition regions had been presented. Such data also might have shed some light on item (d), for which no hypotheses were offered.

Item (c) of their summary, though speculative, appears reasonable. In support of their finding of transition temperatures for phase changes in erythrocytes, the authors noted that Elford and Solomon (1974) had obtained Arrhenius plots for Na- and Rb-influx in dog erythrocytes consistent with the control Na- and Rb-effluxes reported in this study, and had found two linear regions with a transition at 22.4 deg C for Na+ and two linear regions with a transition at 11-13 deg C for K+. Olcerst et al. suggested that the discontinuities in the Arrhenius plots are a result of structural changes at the efflux site and that in the rabbit erythrocyte, transport of Na and Rb may take place at the same locus or loci, and they indicated that a 22.5-deg-C transition was seen in Arrhenius plots of facilitated transport of 3-0-methylglucopyranoside in

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this energy for Rb (corrected for scattered Na counts). The respective MTDAs were 0.37 and 1.12 pCi.

Semilog plots of the average control-efflux activities of Na and Rb at each temperature vs time were made, and the data were fitted by least-squares linear regression to a single exponential model based on the assumption that backflux into RBCs is negligible when hematocrit is less than 0.3%. The authors noted that hematocrit was always less than 0.25% in this study, and that correlation coefficients close to 1.0 were typical. (If the 0.005 ml added to the 1.5 ml of medium were all RBCs, then the hematocrit would be 0.33%.) Best estimates of efflux at 1 hr derived from these plots were used to form Arrhenius plots (log of the 1-hr efflux of each tracer per ml of sample vs the inverse of the absolute temperature) over the temperature range 2.5-37 deg C, to which least-squares lines were fitted. The 1-hr temperature-control efflux values were compared with the 1-hr RFR efflux values, with statistical significance determined by a one-tailed Student's t-test.

The Arrhenius plot for control efflux of Na, presented in Fig. 3 of the paper, exhibited four distinct linear regions, each of negative slope representing the activation energy of the transport process involved, with transitions regions of positive slope between them. From Table II of the paper, the activation energy (in kcal/g-mole) for region 1 (which ranged from 2.5 to 8 deg C) was 46.98; for region 2 (13-21 deg C), it was 36.86; for region 3 (22-35.5 deg C), it was 6.94; and for region 4 (36-37 deg C), it was 23.67. For the transition (8-13 deg C) between regions 1 and 2, the activation energy was -55.17; for the transition (20-22.5 deg C) between regions 2 and 3, it was -90.24; and for the transition (35.5-36 deg C) between regions 3 and 4, it was -205.75. (Note that presentation of the activation energies to 4 or 5 significant figures seems unwarranted.)

Also displayed in Fig. 3 were 1-hr Na-efflux values for samples exposed at various temperatures to RFR at 100, 190, and 390 W/kg. The ratios of RFR-induced efflux to control efflux were displayed in Table I. At a mean temperature of 22.5 deg C (in the transition between regions 2 and 3), 100 W/kg yielded a ratio (+/- SEM) of 2.32 (0.45), 190 W/kg a ratio of 3.29 (0.42), and 390 W/kg, 1.38 (0.33). Thus, the ratio increased with increasing SAR for the first two values, but decreased for the highest SAR. At 13 deg C (in the transition between regions 1 and 2), 390 W/kg yielded a ratio of 10.57 (3.54). At 35.5 deg C, the ratio was 1.78 (0.16) for 190 W/kg; at 36.0 deg C, it was 2.02 (0.27); at 37.0 deg C, it was 2.42 (0.21). The differences between these ratios and unity were all statistically significant. (Values at other SARs for the latter four transition temperatures were not given.)

The corresponding Arrhenius plot for control efflux of Rb, shown in Fig. 4, was similar. From Table III, the activation energies (in kcal/g-mole) were 24.76 for region 1 (7.5-10 deg C), 24.38 for region 2 (13-20 deg C), 13.20 for region 3 (22.5-35.5 deg C), and 50.18 for region 4 (36-37 deg C). For the transition (10-13 deg C) between regions 1 and 2, the activation energy was -17.51; for the transition (20-22.5 deg C)

(outside the waveguide) and connected to a Wheatstone bridge served as a calorimeter that measured the total power absorbed by the sample cell. In Rabinowitz et al. (1977), it was noted that the dielectric constants of Teflon and dodecane are both 2.1, and that the loss factor of dodecane is less than 0.0001 and that of Teflon is less than 0.001. Thus, more than 99% of the RFR energy entering the sample cell was absorbed by the sample.

OTHER INFORMATION: The authors noted that measurements with a Yellow Springs Instrument Company 18-gauge thermistor yielded a difference of 0.5 deg C (presumably between the center of the sample and its surface) at an SAR of 100 W/kg, which corresponded closely with theoretical calculations in Rabinowitz et al. (1977).

Blood samples were drawn from male New Zealand white rabbits, the red blood cells (RBCs) were washed three times with a medium of tonicity 305 mosm that included ouabain (presumably to inhibit the Na+/K+ membrane pump), and the buffy white cell layer was removed by aspiration after centrifugation. RBCs were incubated with Na-22 and Rb-86 as chlorides at respective activities of 18.2 and 0.37 microcuries per ml for 2 hr at 37 deg C. (Rb-86 served as an analog for potassium and offered a longer half-life than any available potassium isotope.) Prior to RFR exposure of RBCs, 1.5 ml of nonradioactive medium was placed in the sample compartment and preheated to a desired average temperature by a combination of dodecane- and RFR-heating. At this time, 0.005 ml of the RBCs incubated with the radio-labeled salts was added, and the sample was exposed to RFR for 1 hr. On termination of exposure, the blood cells and medium were separated by either filtration or refrigerated centrifugation, and hemolysis was measured by both the standard cyanmethemoglobin technique and an extracellular C-14 inulin marker. Hemolysis was not observed in RFR-exposed or control samples (no data presented).

Temperature profiles of passive efflux rates of Na-22 and Rb-86 were first measured in a Gibson Respirometer shaker bath maintained at +/- 0.02 deg C with an immersion refrigeration unit. Subsequent experiments were performed at controlled temperatures ranging from 2.5 to 37 deg C, with those between 20 and 25 deg C done at 1-deg intervals. For each temperature, effluxes from duplicate aliquots of 5 replicate samples were determined at 0.5, 1, 1.5, and 2.5 hr.

The activities of sample filtrates of volume 0.2 ml in 2 ml of distilled water were determined by counting with a Picker NaL (TI) well crystal gamma-ray spectrophotometer. Rb activity was found by correcting the net count in the window from 940 to 1170 keV for scattered Na activity, and Na activity was found by summing the net count in the window from 1170 to 1340 keV. Counting was done for 40 min, which yielded 3000 to 5000 counts in the window regions. Minimum detectable true activities (MDTAs), calculated at the 95% confidence levels for both type I and II errors, were 0.88 and 2.57 pCi for Na and Rb, respectively. Supernatant activities were determined on a Beckman three-channel autogamma counter, with the region above 1170 keV as the Na window and the region below

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Olcerst, R.B., S. Belman, M. Eisenbud, W.W. Mumford, and J.R. Rabinowitz
THE INCREASED PASSIVE EFFLUX OF SODIUM AND RUBIDIUM FROM RABBIT
ERYTHROCYTES BY MICROWAVE RADIATION

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AUTHOR ABSTRACT: The passive efflux rates of sodium-22 and rubidium-86
from the red cells of male New Zealand white rabbits were measured in
vitro after 1-hr irradiations at 2.45 GHz. The temperature of the
samples and the power absorbed were controlled. Arrhenius plots of
measurements made in the absence of radiation exposure revealed that
both the sodium and rubidium efflux have four separate linear regions
with transitions at 8-13, 22.5, and 36 deg C. The efflux rates with
microwave exposure were identical to the control rates, except at the
critical temperatures, where irradiation increased the efflux of both
cations. This response was examined at the 22.5 deg C transition at
three specific absorption rates (100, 190, and 390 mW/g). At all three
levels the cation efflux was statistically greater than one would
predict from a strictly thermal response. The response does not
increase monotonically as a function of absorbed power. Similar
increased cation efflux was also observed near the 36 deg C and 8-13 deg
C transitions. Possible mechanisms for this effect are discussed.

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Study Type: Cellular and Subcellular Effects, Immunology and
Hematology, Physiology and Biochemistry; IN VITRO; RABBIT
Effect Type: RFR-induced alteration of hemolysis and efflux of sodium
and rubidium ions out of rabbit erythrocytes
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not indicated
SAR: 100, 190, and 390 W/kg

EXPOSURE CONDITIONS: Exposures to RFR were done in a system described
by Rabinowitz et al. (1977). The sample cell consisted of two
concentric cylindrical Teflon compartments. The inner compartment
served to hold a 1.5-ml sample. The coolant dodecane was circulated
through the outer compartment, and its temperature was maintained to
within +/- 0.02 deg C in a temperature-controlled Haake FKP bath. The
sample cell was inserted transversely into the center of a section of
WR-430 rectangular waveguide along the direction of maximum electric
field (for the TE10 mode). The waveguide was terminated with a sliding
short that was adjusted to locate the sample at the peak of the
standing-wave electric field (a quarter wavelength from the short). A
bidirectional coupler and a tuner between the sample cell and the RFR
source (a 2.45-GHz diathermy generator) were used for determining
forward and reflected powers and for impedance matching, respectively.

Matched thermistors mounted in the coolant inflow and outflow pipes

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The absence of hemolysis and K+ release for human RBCs heated to 37 deg
C can be taken as an indication that RFR-induced changes in rabbit blood
may not be reflected in similar effects with human blood.

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EXTRACORPOREAL HEMOLYSIS OF BLOOD IN A MICROWAVE WARMER
New England J. Med., Vol. 285, pp. 317-319 (1971)

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higher, respectively, than for the RT group, as contrasted with ratios of only 1.7 and 1.4 for the samples heated to 37 deg C.

In their summary, the authors noted that heating rabbit RBCs to 37 or 41.5 deg C by either RFR exposure at various frequencies or conventional means along approximately the same temperature profile yielded increased hemolysis and K+ efflux, as compared with RBCs held at room temperature. They also indicated that the effects were absent when RBCs were heated by only 3.7 deg C (with 2.45-GHz RFR at 10 mW/sq cm).

CRITIQUE: A minor point regarding the exposure arrangement for 2.45 GHz was that the start of the conventional far-field region (twice the square of the larger dimension of the horn aperture divided by the wavelength) is (for the horn aperture 34.5 x 49.5 cm) about 400 cm, so for the 137-cm used, the samples were in the near field of the horn, not its far field as stated. However, the normalized SAR obtained for 2.45 GHz with the rotating holder evidently represented the spatial average of all sample directions relative to the fixed E vector, so it seems unlikely that this point was significant biologically. (The 10-cm distance used for the Ku region was well within the far field of the 2.0 x 2.5 cm horn at any of the frequencies. As noted previously, however, the authors did not provide any SAR data for the Ku region). In any case, the results of this study clearly indicate that the effects observed were thermally induced, with a threshold SAR well above 46 W/kg (10 mW/sq cm at 2.45 GHz).

The authors noted that their results were in agreement with those of Liu and Cleary (subsequently published as Liu et al., 1979), who reported no significant differences in loss of Hb or K+ from rabbit RBCs heated to 37 deg C by 2.45-, 3-, or 3.95-GHz RFR or conventional techniques, and with similar results of Hamrick and Zinkl (1975) with 2.45- and 3 GHz and conventional heating. However, the authors indicated that their findings differed from those of Baranski et al. (1971, 1974) and Ismailov (1971), who reported increased hemolysis and efflux of K+ from rabbit RBCs exposed to 1- or 3-GHz RFR at power densities as low as 1 mW/sq cm.

One possibility suggested by the authors was that Baranski et al. and Ismailov had resuspended their RBCs in a simple unbuffered saline whereas the authors used a veronal-buffered saline solution containing divalent cations and gelatin, designed by Kabat and Meyer (Kabat, 1961) to reduce erythrocyte fragility and to provide the RBCs with a more natural environment. On the other hand, the authors noted that, based on some of the results of Hamrick and Zinkl (1975), such differences cannot account for the discrepancies, and suggested instead that mixing the samples during exposure (such as by rotation) might have avoided local hot spots. In support, they cited Staples and Griner (1971), who reported increased hemolysis in unrotated blood bags heated to 30.7 deg C by exposure to 2.45-GHz RFR and no increase in similarly exposed rotated bags. The hot-spot hypothesis seems valid. Presumably the temperature increase obtained by Staples and Griner in the rotated bags was below the threshold for increased hemolysis.

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BIOCHEMISTRY
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Ortner, M.J., M.J. Galvin, and R.D. Irwin
THE EFFECT OF 2450-MHZ MICROWAVE RADIATION DURING MICROTUBULAR
POLYMERIZATION IN VITRO

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AUTHOR ABSTRACT: Exposure to 2450-MHz (cw) microwave radiation causes
inhibition of cell division in intact cells and varied in vivo
biological effects in both avian and mammalian species. Because these
reported effects may result from alterations in the dynamics of
microtubule formation, we studied the effects of simultaneous microwave
exposure (2450 MHz, cw) during each of the three critical stages of the
intracellular polymerization cycle. In addition, using circular
dichroism spectroscopy, we studied the effect of microwave irradiation
on the secondary structure of purified tubulin polypeptides. These
studies were accomplished using specially constructed exposure systems
that permit the continuous recording of turbidometric or circular
dichroism measurements during simultaneous exposure to microwaves.

The baseline turbidity of microtubular protein did not change under the
influence of microwave radiation (20 or 200 mW/g SAR) and irradiation
had no effect on the light-scattering properties of the depolymerized
protein. EGTA-induced polymerization and cold-induced depolymerization
patterns were also similar for both control and microwave-irradiated
samples. The circular dichroism spectrum of purified tubulin also did
not appear to be influenced by microwave irradiation, indicating a lack
of effect on the protein secondary structure. The data suggest that the
cellular effects of microwaves are not due to changes in microtubular
proteins or their rate of polymerization.

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Study Type: Cellular and Subcellular Effects, Physiology and
Biochemistry, Mechanisms of Interaction; IN VITRO; CALF
Effect Type: RFR-induced alterations of microtubular-tubulin dynamics
(changes in polymerization and depolymerization rates)
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not measured
SAR: 20 or 200 W/kg

EXPOSURE CONDITIONS: The sample chamber was a quartz cylinder inserted
in a direction of maximum E field of a fluid-filled waveguide section.
The impedance of the waveguide was matched to that of air by a quarter-
wave dielectric slab. Sample temperature during exposure could be held
at 37 deg C by circulating a water-glycerol mixture through a jacket
around the chamber from an external bath kept constant at 38.5 deg C.
For exposure at 200 W/kg, the temperature of the external bath was set
to 35 deg C to offset sample heating by the RFR. The sample temperature

could also be lowered to 4 deg C within 1-2 min by circulating water-glycerol mixture from a bath held at -4 deg C through the jacket. The cooling process could be reversed. During exposure, samples were stirred magnetically (with a stirrer in one end of the cylinder outside the waveguide) and their temperatures were monitored continuously with a nonperturbing Vitek probe. SARs were determined from time-temperature profiles measured under identical conditions without temperature control.

For the experiments on light scattering from microtubular protein, monochromatic light at about 380 nm was conveyed to the sample by a nonfluorescent quartz fiber-optic cable passed through the waveguide wall and fastened to the sample compartment with a Plexiglas holder. Light scattered from the sample was directed via a similar cable to a photomultiplier and amplifier through a 520-nm filter, the latter to attenuate the scattered light to the maximum sensitivity range of the instrument. To increase the signal-to-noise ratio of the scattered light, the amplified signal was also averaged by feeding it into a polygraph whose upper frequency response was set to 0.08 Hz.

For circular-dichroism measurements of purified tubulin, a spectropolarimeter was modified to accept a similar sample-exposure system.

OTHER INFORMATION: The authors noted that in a previous study (Ortner et al., 1981), they had found that 2.45-GHz RFR at 600 W/kg affected the secondary structure of human erythrocyte spectrin, a reversible effect, but were unable to correlate the change with any change in spectrin function. The purpose of the present investigation, therefore, was to determine whether such reversible changes comprised a generalized effect of RFR on large macromolecular assemblies, exemplified by microtubules.

As indicated by the authors, microtubules are hollow, cylindrical organelles found as an extensive filamentous network in the cytoplasm of nondividing cells, and that the major component of the microtubular wall is a 6S, 110,000-dalton protein called tubulin. They indicated that under proper in-vitro conditions (37 deg C in the presence of guanosine 5'-triphosphate), purified tubulin and accessory proteins assemble or polymerize into microtubules that appear to be morphologically identical with those studied in vivo. Cooling to 4 deg C or the addition of Ca++ causes the assembled microtubules to depolymerize back into 6S tubulin and oligomers.

In this study, microtubular protein was purified from fresh calf brains by successive cycles of polymerization and depolymerization, and the protein was determined by the Biuret method with bovine serum albumin as a standard. Tubulin was separated from the accessory proteins by chromatography. The purities of the microtubular-protein and purified-tubulin preparations were determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

In the light-scattering experiments, samples of depolymerized cycle-purified microtubular protein were incubated and exposed at 200, 20, or 0 W/kg for 10 min, during which sample temperature was maintained at 37 +/- 0.3 deg C. Following exposure, polymerization was initiated by adding ethylene glycol-bis (B-amino ethyl ether) tetraacetic acid (EGTA) and guanosine 5´-triphosphate (GTP). At 12-15 min after polymerization initiation, the samples were cooled to 4 deg C by circulating water-glycerol mixture at -4 deg C through the jacket, to depolymerize them. Turbidity was monitored with the photomultiplier instrumentation during exposure, polymerization, and depolymerization.

The results of a typical experiment with a sample exposed at 20 W/kg were presented graphically in terms of the light scattered by the sample vs time. The ordinate was the ratio of the light scattered at each instant to the light scattered 12-15 min after completion of the 10 min of exposure (just before cooling was begun). (This time was selected because polymerization was found to have stabilized by then). After signal averaging, the data showed a ratio of 0 during the 10 min of RFR exposure, i.e., turbidity was not affected during exposure. During the 12-15 min following the addition of EGTA and GTP for polymerization, the scattering ratio rose essentially linearly with time from 0 to 1. The ratio returned to 0 within about 2 min after cooling was begun.

A summary of the results of the scattering experiments at 200, 20, and 0 W/kg (7-10 runs at each level) was exhibited graphically as the percentage of maximum light scatter (with SEM bars) vs time. For all three levels, a relatively steep rise in percentage occurred during the first 2 min after the addition of EGTA and GTP, followed by a basically linear rise at a slower rate to saturation at 12-15 min. The authors stated: "The data show that microwave radiation at power levels up to 200 mW/g SAR had no observable effect on the nucleation or elongation of microtubules in vitro." However, during the slower rise, the curve for exposure at 200 W/kg was slightly above that for exposure at 20 W/kg and the latter curve was slightly above that for 0 W/kg. Presumably the differences among the three curves at corresponding times were not statistically significant.

Data on the effect of exposure at 200, 20, and 0 W/kg on temperature-induced depolymerization were presented graphically as the percentage of maximum light scatter (with SEM bars) vs progressively lower cooling temperature. All three curves were "reverse-S" shaped, showing slight turbidity diminution from 100% in the temperature range from about 30 to 20 deg C followed by steep drop to 0% at about 4 deg C. The differences among the curves were minor and were ascribed to a difference in cooling rate for the samples exposed at 200 W/kg.

The results for the circular-dichroism experiments showed no significant differences in optical activity between purified tubulin exposed at 200 and 0 W/kg. Moreover, high-resolution measurements of optical activity in the region of aromatic amino acid absorption showed no effect of RFR exposure.

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In their discussion, the authors indicated that the findings of this study extended those of a previous one (Paulsson et al., 1977), in which no effect on the final development of the microtubule elongation process was observed from exposure to 3.1-GHz pulsed RFR. They noted that the instrumentation used in the earlier study did not permit measurements of the effect of RFR on the critical nuceation phase of polymerization, depolymerization, or the rate of elongation.

Citing appropriate references, the authors stated: "In vivo, microtubule assembly and disassembly occur at precise times in the cellular reproductive cycle, and it has been suggested that the dynamic exchange of subunits on and off microtubules may influence the movement of chromosomes during mitosis. Microtubule-tubulin dynamics are also important in axonal transport, and the extremely high concentration of microtubular protein in the brain strongly implicates microtubules in nervous-system function. Microwave radiation has been shown in vivo to affect many biological functions that may involve microtubule dynamics as outlined above." However, they then stated:

"The entire process [of polymerization and depolymerization] appears to be unaffected by microwave field intensities high enough to increase the ambient temperature (from 34 to 37 deg C). This would indicate that the energy deposited within the sample chamber was sufficient to affect the solvent water and possibly protein-bound water molecules. Since the association of tubulin molecules to form the microtubule wall involves a loss of ´bound´ water, it might be expected that microwave radiation could influence polymerization or perhaps the critical protein concentration required to support polymerization. However, we also found that the critical protein concentration needed for polymerization was unchanged by irradiation." They then concluded that: "A molecular basis for the reported effects of microwave radiation on biological systems will probably, therefore, be found in some other aspect of cellular physiology."

CRITIQUE: The negative results of this investigation and the conclusions of the authors appear to be correct. However, this in-vitro study was done on extracted microtubule samples in the absence of cell membranes and their interactions with intracellular and extracellular components, so the relevance of the findings (though negative) to effects of RFR on intact cells is open to question. Moreover, others (notably Adey, 1981, cited in this paper) have reported that direct effects of RFR fields on cells can and does occur at the membrane level. If feasible, it would be interesting to seek possible effects of RFR exposure on microtubules in intact cells suspended in appropriate media.

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Radiat. Res., Vol. 70, pp. 212-223 (1977)

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Wright, N.A., R.G. Borland, J.H. Cookson, R.F. Coward, J.A. Davies, A.N.
Nicholson, J.L. Christie, N.G. Flanagan, and V.D. Goodridge
BIOLOGICAL STUDIES WITH CONTINUOUS-WAVE RADIOFREQUENCY (28 MHZ)
RADIATION

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AUTHOR ABSTRACT: Effects of high-frequency (28 MHz) continuous-wave
radiation have been studied in the rat and monkey. No histopathological
(rat--125 mW/sq cm for 28 days) or hematological (monkey--25 mW/sq cm
for 24 days) changes could be attributed to the radiation. In the
monkey, (125 mW/sq cm for 11 days) there was an increase in urinary
calcium concentration which was most likely due to restricted movement.
In the rat (220 mW/sq cm for 13 days) there was reduced uptake of iodine
by the thyroid, lower levels of plasma thyroid-stimulating hormone, and
reduced ratio of protein bound to nonprotein bound iodine. Food
consumption was also decreased. The changes are likely to have arisen
as a compensatory response to an induced heat load. A nonthermal effect
of continuous-wave high-frequency radiation has not been shown in this
study. The effects were likely to be associated with either
physiological compensation for induced heating or restriction of
movement.

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Study Type: Physiology and Biochemistry, Immunology and Hematology,
Endocrinology; IN VIVO; MACACA FASCICULARIS, MACACA MULATTA, RAT
Effect Type: RFR-induced physiologic, histopathologic, and
endocrinologic changes
Frequency: 28 MHz
Modulation: CW
Power Density: 25, 125 mW/sq cm (primates); 125, 220 mW/sq cm (rats)
SAR: Not stated; estimated as 0.1, 0.5 W/kg in primates and 0.3, 0.5
W/kg in rats

EXPOSURE CONDITIONS: Exposures were done in two chambers, a large one
designed primarily for primates but used for rats as well, and a smaller
one used only for rats. Both chambers were housed in a room that was
air-conditioned, with the temperature set at 70 +/- 3 deg F and the
relative humidity at 55 +/- 5%. A separate (small) chamber was
available for sham-exposures of rats but not for primates.

The large chamber was a rectangular coaxial TEM cell fed, by circular
coaxial line through a tapered section, from a 30-kW HF (2-28.9 MHz)
transmitter, and similarly terminated with a 10-kW load. Primates were
exposed concurrently in groups of up to eight, each in its own 0.6-m x
0.6-m x 0.6-m cage constructed of nonconducting materials, by inserting
the cages in four rows of two each into the chamber. The separation
between cages was about 0.4 m. Thruline power meters in the feed line
were used to measure forward and reflected powers, and another power

meter in the termination line was used to measure transmitted power.
The center electrode was horizontal, providing a vertically polarized
field. The standing-wave ratio at the input to the TEM line was less
than 1.05 both empty and with primates present within cages. Waste
water and urine were collected separately from each chamber. Buildup of
humidity because of air-circulation restriction by the horizontal center
electrode of the TEM line was overcome by a laminar flow system along
the length of the electrode. Exposures of rats in this chamber are
described later.

The smaller chamber was also a TEM system. However, the center
electrode was vertical, to provide a horizontally polarized field.
Housing arrangements for the rats were different for each experiment.

OTHER INFORMATION: Analysis of variance (ANOVA) was used on the data.
The assumptions of ANOVA were examined in each case by plotting
residuals vs fitted values. Where appropriate, the variates were
transformed to satisfy the assumptions of ANOVA adequately. Subsequent
comparisons were made with t-tests for a subset of the possibilities
using least-significant differences.

For hematologic studies, 6 cynomolgus monkeys (Macaca fascicularis)
weighing 2.2-2.8 (mean 2.4) kg were acclimated in the exposure chamber
for 7 days, after which they were exposed at 25 mW/sq cm for 24 days, 23
hr per day. Water was provided once per hr with an isolated drip
system, at which time the RFR was removed for 1 min to prevent shock.
The RFR was switched off 1 hr/day for cage cleaning, after which the
monkeys were fed. Two other monkeys (mean weight 2.4 kg) caged in their
usual housing facilities served as controls. Blood samples were taken
and bone marrow was aspirated from each of the 8 monkeys about 2 weeks
before exposure, twice during exposure, and 2 weeks after exposure. The
samples were subjected to: full blood count, platelet count, peripheral
blood smear examination, iliac crest marrow smear examination including
stain for iron, and the platelet aggregation test. In addition, the
fcllowing tests were performed: serum B12 and red folate assays;
prothrombin time and activated partial thromboplastin time; reticulocyte
count on peripheral smear; and a biochemical screen for serum glutamic
oxaloacetic transaminase, alkaline phosphate, bilirubin, creatinine,
uric acid, urea, phosphate, calcium, albumin, total protein, potassium,
and sodium.

The authors indicated (without presenting data) that: no RFR-induced
abnormalities were found, there were no changes in full-blood or
reticulocyte counts or in coagulation, and all marrow samples showed
considerable activity with normal maturation in each of the cell series.
They also noted that at no time was dyshemopoiesis observed and that
iron stores remained adequate and stable. They did indicate the
occurrence of mild leukosis, relative to preexposure levels, in both
RFR-exposed and control animals. Tests for platelet microaggregates
showed no significant change, but 1 exposed monkey exhibited a slight

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increase in platelet aggregation with a quick return to normal. Red-cell folate, B12 levels, and biochemical parameters remained unchanged, and there was no evidence of renal or hepatic dysfunction.

To study the effect of RFR exposure on urinary electrolyte levels, 8 rhesus monkeys (Macaca mulatta) weighing 4.6-6.2 (mean 5.7) kg were acclimated to the chamber for 4 weeks. The experiment proper consisted of a 5-day control period, 11 days of exposure at 125 mW/sq cm, and a 5-day recovery period. Urine was collected on an individual timed-sample basis over 23 hr of each day and analyzed for chloride, sodium, potassium, and calcium.

The daily volumes of urine excreted (in ml) and the total masses of each electrolyte (in mg) were averaged over control days 1-5, exposure days 7-11, exposure days 12-16, and recovery days 17-21. (The values for day 6 were excluded because of a failure in the watering system.) The results, given in their Table I, showed significant (p<0.05) increase in urine output during exposure. The means were 2389, 2924, 3043, and 2737 ml for the respective periods, with a pooled standard error (SE) of 180.83 ml taken from the analysis of variance. The changes in excretion of sodium, potassium, and chloride were nonsignificant. The mean totals of sodium for the four successive periods were 1466, 1671, 1526, and 1416 mg, with a pooled SE of 76.74 mg; the means for potassium were 2957, 3100, 3215, and 2999 mg, with a pooled SE of 177.16 mg; the chloride values were 5651, 6699, 6734, and 6118 mg, with a pooled SE of 370.29 mg. The differences were not significant (p>0.05).

An increase in mean calcium excretion (relative to control level) during the first exposure period was significant (p<0.001), as were increases during the second-exposure and recovery periods (p<0.05). The means for the four periods were 87.2, 165.3, 126.8, and 133.6 mg, respectively, with no pooled SE given. However, the authors noted that they log-transformed the calcium values prior to analysis of variance to stabilize the variance, which yielded means of 2.5088, 3.3374, 3.0253, and 3.0522 for the respective periods, with a pooled SE of 0.1371.

Young adult male Wistar rats with an initial mean body weight of 175 g were studied for possible RFR-induced pathology, 40 rats comprising the RFR-exposure group and 32 the sham-exposure group. The rats were housed in Perspex cages, 8 rats per cage. The RFR group was placed beneath the center electrode of the large exposure chamber, a location that tended to confine the exposure to the H or K plane. The rats were exposed 23 hr per day at 125 mW/sq cm for up to 4 weeks. Sham-exposures in the same chamber were completed first. Water was provided by a drip system and Porton Rat Diet was available ad libitum. After exposure, the rats were euthanized by cervical dislocation in groups of 4 at 2- or 4-day intervals during the 4-week period. Whole-body weights and the weights of the thymus, heart, lungs, spleen, adrenals, kidneys, testes, and brain were recorded. These organs were examined histologically, as were the stomach, small and large intestines, pancreas, skeletal muscle, bone, bone marrow, and skin with subcutaneous tissue. Tissues were also fixed in glutaraldehyde and osmium tetroxide, embedded in resin, sliced,

and stained for electron-microscopic examination. Such examination was done on 10% of each tissue except bone and bone marrow.

Visceral congestion was evident in both 25 sham-exposed and 32 RFR-exposed rats euthanized from day 4 onward (about 80% of each group). Histologic examination of the lungs showed numerous small, focal hemorrhages on the pleural surfaces, and areas of pulmonary atelectasis and intraalveolar hemorrhage consistent with the gross appearance of the lungs. The surface of the liver was mottled, presumably due to focal vascular congestion. The cut surfaces of the kidneys showed congestion at the cortico-medullary junction and in the medulla.

One tumor, a nodular protuberance about 1 cm in diameter on the anterior surface of the liver, was found in an RFR-exposed rat killed on day 26. The architecture of the tumor was near-normal and resembled an area of focal nodular hyperplasia. There was no evidence of destruction of neighboring tissue, of dissemination, or of any malignancy. There were "dark cells" in the liver, but in 2-micron sections lightly stained with hematoxylin and eosin, such cells were found in both RFR- and sham-exposed rats. With electron microscopy, hepatocytes from both groups were smaller than normal and contained large numbers of mitochondria.

No data on body or organ weights were presented. However, the authors indicated that weights increased linearly with age in all rats, and that when organ weights per 100 g of body weight were plotted vs days of exposure, only three measures fell outside the limit of two standard deviations, the latter data from RFR-exposed rats. The ratio of brain-to-body weight on days 3 and 4 and spleen-to-body weight on day 4 were higher for the RFR group than the sham group.

For studies of thyroid function, 32 pairs of male Wistar rats matched genetically and for body weight (mean 225 g) were used. One of each pair was housed in an individual Perspex cage within the small exposure chamber (at a location that tended to confine exposure parallel to the E field), and the other rats were similarly housed in the sham-exposure chamber. Porton Rat Diet was available ad libitum up to 40 g per day. About 10 ml of water was pumped to each rat through narrow-bore plastic tubes every 30 min for 30 seconds, during which time the RFR was shut off.

In the study proper, the two groups were acclimated to their chambers for 14 days. This interval was followed by a 5-day control period, to assess comparability between the groups, and a 13-day period of exposure at 220 mW/sq cm or sham-exposure for the respective groups (presumably for 23 hr/day). Thyroid function was tested at intervals of 2 or 3 days during the 18-day period by the 24-hr uptake and turnover of I-125. On the day before each test, 4 rats of each group were injected i.p. with 5 microcuries of sodium iodide (I-125). About 24 hr later (between 0900 and 0915 on the test day), these rats were euthanized by decapitation, and rectal temperatures were recorded within 2 min. Whole blood was collected in 10-ml tubes containing 1 mg of ethylenediaminetetraacetate (EDTA). Hematocrit and hemoglobin were assayed immediately, and the

whole blood was centrifuged for 10 min at 670 g. The protein-bound I-125 component of plasma was precipitated. Plasma samples from each rat were frozen at -20 deg C for subsequent assay of levels of thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4). Thyroid glands were weighed and suspended in saline containing sodium thiosulfate. The I-125 radioactivities of the thyroid glands, plasma, and protein-bound samples were determined by counting.

The results for each group were presented in Table II as means for 12 rats (without SEs or SDs) for the control period, the first week, and the second week of RFR- or sham-exposure. The authors noted that the analyses were performed on log transformations of the actual data values. Mean values of total food consumption by the sham group during the respective periods were 27.0, 29.4, and 30.8 g, a significant ($p < 0.05$) linear increase, as would be expected for growing animals. Food intake by the RFR group remained essentially constant. The successive means were 26.5, 27.0, and 26.3 g, with the last value 14.6% lower ($p < 0.05$) than the corresponding value for the sham group.However, the increases in body weight of both groups were similar. The authors indicated (without presenting data) that there were no significant differences in thyroid weight, rectal temperature, hematocrit, or hemoglobin between the groups.

Several indices of thyroid function were changed in the exposed group. Uptake of I-125 in the thyroid, the ratio of I-125 in the thyroid to I-125 in plasma, and the ratio of protein-bound I-125 to I-125 in plasma were lower, and plasma TSH tended to be lower, in the RFR group than the sham group. The specific values presented in Table II are reproduced below. Significance levels were given for some RFR-group values, presumably by comparison with the sham-group values for the corresponding periods. These significance levels are shown below in parentheses immediately after their respective RFR values.

The mean uptakes, by the sham group, of I-125 in the thyroid for the three periods were 19.6%, 21.6%, and 26.1% (of dose). The corresponding values for the RFR group were 20.4%, 18.1%, and 19.7% ($p < 0.05$). The ratios of thyroid I-125 to plasma I-125 for the sham group were 14.1, 14.2, and 20.9, and the corresponding values for the RFR group were 16.4, 10.3 ($p < 0.05$), and 12.2 ($p < 0.001$). The mean ratios of protein-bound I-125 to plasma I-125 for the sham group were 0.71, 0.87, and 1.14; those for the RFR group were 0.66, 0.69, and 0.85 ($p < 0.05$). Mean protein-bound I-125 cpm/ml for the sham group were 502, 668, and 715; the values for the RFR group were 489, 703, and 738 (none labeled significant). TSH concentrations in plasma for the sham group were 472, 668, and 636 micrograms/ml; those for the RFR group were 462, 589, and 454 ($p < 0.1$, presumably regarded as near the borderline of significance). T4 concentrations in plasma for the sham group were 3.52, 2.51, and 3.53 micrograms/100-ml; those for the RFR group were 2.06 ($p < 0.001$), 2.26, and 3.11 ($p < 0.05$). T3 concentrations in plasma for the sham group we e 0.20, 0.21, and 0.41 nanograms/ml; the corresponding values for the RFR group were 0.56 ($p < 0.01$), 0.59 ($p < 0.001$), and 0.54.

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In their discussion, the authors stated: "In conclusion, the present studies have shown that exposure of monkeys to HF radiation at low levels of absorbed power does not modify the hemopoietic system. Though calcium excretion was modified, we feel that this was unlikely to be caused by exposure, and was probably due to restricted movement. Further, subsequent pathological examinations revealed no changes which could be ascribed to radiation, and it is likely that thyroid function is only modified in response to an imposed heat load. Extrapolation of these data to man, as far as this is feasible, would suggest that HF radiation at levels below that expected to give rise to thermal changes is unlikely to lead to significant effects, and so the studies would not support a decrease of current levels used as safety standards for continuous wave exposure to frequencies in the HF band." They offered the following surmises:

"The transitory change in platelet aggregation in one monkey is considered to be a chance finding and unlikely to be related to exposure. Vascular congestion in some organs and pulmonary hemorrhaging found in both groups of rats are likely to have been a consequence of the method of killing. Though hematological and pathological changes have been reported after exposure to HF band radiation (Prince et al., 1972; Henny et al., 1970; Zubkova-Mikhailova and Alekseev, 1968), these studies involved high levels of power, and so our negative findings are in agreement with those of Bollinger (1971) and Krupp (1978) involving exposures of 100-1250 mW/sq cm."

"In the present studies, the possibility that exposure led to a persistent increase in calcium excretion cannot be excluded, but since the animals had been confined in smaller cages than usual [each cage a 0.6-m cube] for 5 weeks before the period of radiation, it is more likely that the increased calcium excretion was due to prolonged restriction of movement. Immobilization leads to elevated urinary calcium levels, and the changes found in the present studies are compatible with this explanation though they were far less than those which had been observed in primates severely restricted in a simulated space capsule (Co_kett et al., 1972)."

"As far as thyroid function is concerned, local absorption by the gland in the absence of pituitary control leads to an increase in hormone production (Magin et al., 1977b), whereas whole-body exposure to thermal levels (Lu et al., 1980b; Parker, 1973) has been shown to reduce thyroid hormone secretion. In the present study reduced thyroid activity, as indicated by lower thyroid iodine and plasma TSH levels, was accompanied by a fall in food consumption, and so it is likely that there was a reduction in metabolic heat production in response to the absorbed energy. However, the analysis of T3 and T4 levels during the exposure period was complicated by differences between sham and exposed groups during the preexposure week, and so any possible effects of radiation cannot be inferred from these values. Though both groups of rats were treated identically as regards temperature, lighting, and humidity, the sham-exposure chamber was situated near the entrance to the laboratory, and it is possible that the experimenters entering in the morning

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constituted a short-lived stress, affecting the relative concentrations of plasma T3 and T4 due to transient changes in protein binding. Thyroidal iodine and plasma TSH concentration are more likely to represent the actual level of thyroid function, and do indeed indicate a reduction due to radiation. The decrease in plasma TSH levels would suggest that lower thyroid activity may have been initiated at the pituitary level, though negative feedback mechanisms could also have been involved."

CRITIQUE: SARs in the animals corresponding to the power densities used in each part of the study were not explicitly stated. Based on data for a live sitting rhesus monkey in Durney et al. (1978), p. 113, the reviewer calculated that the SARs corresponding to exposure at 25 and 125 mW/sq cm would be roughly 0.1 and 0.5 W/kg, respectively. Also, from pp. 94-95 of Durney et al. (1978) for prolate-spheroidal models of a small and medium rat, exposures at 125 and 220 mW/sq cm would correspond to SARs of 0.25 and 0.4 W/kg.

Instead of presenting such SARs, the authors used calculated and experimental data from Allen et al. (1976) and Durney et al. (1978) to estimate the corresponding exposure levels at 28 MHz in humans. They qualified the procedure with: "Caution must be used when extrapolating the results of the present study to man... These calculations only indicate a theoretical value for whole-body absorption, and localized power deposition may be different (Guy et al., 1976). It has been shown that narrow parts of the body, for example the neck and ankles, are potential ʹhot spotsʹ due to constriction of induced electric current density (Guy et al., 1976)." Their estimates of human SARs for the histopathological and hematological studies were 0.03 and 0.06 W/kg, respectively, corresponding to 1 and 3 mW/sq cm. The latter values are respectively below and above the current ANSI (1982) guideline of 1.15 mW/sq cm for human exposure at 28 MHz. Their estimated SARs for the thyroid and electrolyte studies were 0.5 and 0.3 W/kg, corresponding to 25 and 14 mW/sq cm.

Such interspecies extrapolations are highly questionable because of physiological and morphological differences among species. Moreover, in view of the presence of uncontrolled non-RFR factors evident not only in the quotations above from the paper but also in the occurrence of visceral congestion, lung changes, and other abnormalities in both RFR and sham groups, little if any significance can be given to either the positive or negative findings of this study.

In other studies, notably by Abhold et al. (1981), exposure of rats to 2.45-GHz RFR at 2 and 10 mW/sq cm (0.44 and 2.2 W/kg) had no effect on thyroid function, as measured by the levels of serum T4, T3, T3 uptake, and free thyroxine index. These results were consistent with those of Lu et al. (1980b), who exposed rats to 2.45-GHz-RFR for 2, 4, or 8 hr at power densities in the range 1-70 mW/sq cm (0.21-14.7 W/kg). Among the findings were: increases of colonic temperature at 20 mW/sq cm and higher, inverse relationships between corticosterone and thyrotropin or growth hormone after exposure for 1 hr at 50 mW/sq cm and higher, and

ibition of pituitary-thyroid function after exposure at 20 mW/sq cm
2-8 hr. They indicated that changes in other hormones were
nsient or inconsistent. They noted that exposures for 2, 4, or 8 hr
luded substantial parts of the circadian cycle, a point not addressed
the present study. However, comparison of such results with those of
present study may not be appropriate because of the large difference
frequency (28 MHz vs 2.45 GHz).

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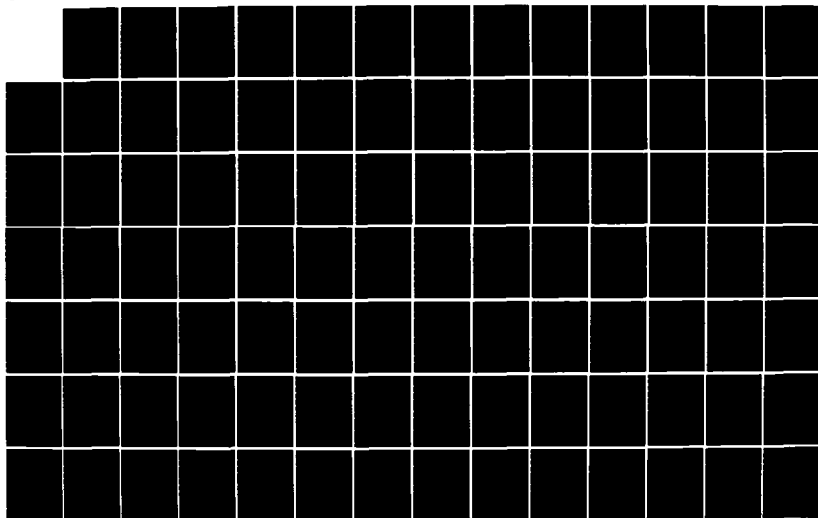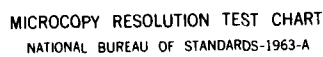
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Ortner, M.J., M.J. Galvin, and D.I. McRee
STUDIES ON ACUTE IN VIVO EXPOSURE OF RATS TO 2450-MHZ MICROWAVE
RADIATION--I. MAST CELLS AND BASOPHILS
Radiat. Res., Vol. 86, pp. 580-588 (1981)

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AUTHOR ABSTRACT: Eight-hour continuous exposure to 2450-MHz microwave
radiation in rats was carried out at incident power densities that cause
no apparent temperature increase (2 and 10 mW/sq cm). The peritoneal
mast cells were unchanged in their viability, percentage, toluidine blue
metachromasia, histamine content, or size. Isolated mast cells from
control and irradiated rats responded in a similar manner to drugs that
stimulate histamine secretion via both the chemical (compound 48/80, a
condensation product of p-methoxy-N-methyl phenethylamine and
formaldehyde) and immunological (concanavalin A) pathways. The release
of histamine in vivo from basophils and mast cells was determined by
intravenous injection of 48/80 into anesthetized rats. Rats subjected
to both levels of irradiation were similar to the controls in their
initial blood pressures and their hyposensitive response to 48/80. We
have thus shown that the microwave frequency and power densities used in
these experiments do not impair normal function in the histamine-
secreting cells of the rat.

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Study Type: Immunology and Hematology, Physiology and Biochemistry,
Cellular and Subcellular; IN VIVO; RAT
Effect Type: Effects of acute in-vivo RFR exposure on basophils and
peritoneal mast cells
Frequency: 2.45 GHz
Modulation: CW
Power Density: 2, 10 mW/sq cm
SAR: 0.44, 2.2 W/kg

EXPOSURE CONDITIONS: Groups of 8 male CD rats (mean weight 300 +/- 35
g) were concurrently sham-exposed or exposed for 8 hr at 2 or 10 mW/sq
cm in individual Styrofoam cages arranged in an oval pattern around the
axis of, and 155 cm below (in the far field of), a standard-gain horn.
The horizontal dimensions of the cages were 10x20 cm, with the latter
oriented parallel to the E-vector. The narrower dimension did not
permit the rat to orient itself comfortably perpendicular to the E-
vector and the vertical dimension (13 cm) permitted the rat to rear but
not stand upright. The top and bottom of each cage were plastic
gratings to allow for ventilation and removal of urine and feces.

Exposures were done within an anechoic chamber maintained at 24 deg C
and 65% relative humidity, and lighted from 6 am to 6 pm. At the
nominal mean power density of 10 mW/sq cm, the values around the oval
ranged from 8.1 to 10.9 mW/sq cm. For exposures at this mean value,
additional fans at cage level were operated to prevent heating from the

RFR absorber under the cages. SARs were determined from Durney et al. (1978), based on a prolate-spheroidal model. For a 320-g rat parallel to the E-vector, the SARs corresponding to 2 and 10 mW/sq cm were 0.44 and 2.2 W/kg. Such calculations were subsequently corroborated by calorimetric measurements (Smialowicz et al., 1979).

The rats were weighed immediately before and after RFR- or sham-exposure. Prior to exposure, they were kept within the anechoic chamber for at least 12 hr in group cages with food and water available ad libitum. They were then transferred to individual cages and the 8-hr exposures were started at 12:30 am, with food and water withheld. Exposures at 0 (sham), 2, and 10 mW/sq cm were conducted on successive days, for a total of 12 experiments.

OTHER INFORMATION: This study was the first in a series involving exposures of rats to 2.45-GHz RFR for 8 hr. The second study was by Abhold et al. (1981) on the effects of exposure on thyroid and adrenal hormones, and the third, by Galvin et al. (1982b), was on the effects of exposure on biochemistry and hematology.

Within 5-15 min after exposure, 6 of the 8 rats of each group were decapitated and peritoneal mast cells were extracted in Locke's solution. The cells from pairs of rats were pooled to make 3 groups of cells per experiment. Each group of cells was diluted to 100,000 mast cells per ml of Locke's solution and divided into two equal subgroups, one subgroup for determining histamine release from mast cells induced by concanavalin A (Con A) and the other for histamine release induced by compound 48/80 (a condensation product of p-methoxy-N-methyl phenethylamine and formaldehyde). For this purpose, both subgroups were incubated at 37 deg C for 10 min, one with 10 micrograms/ml of phosphatidyl serine micelles (PSM), and the other without PSM. Aliquots of cells with PSM were added to serial dilutions of Con A, the PSM being necessary to evoke Con-A-induced histamine release by the mast cells. However, PSM inhibit 48/80, which acts via a separate pathway than Con A, so cells without PSM were added to serial dilutions of 48/80.

Histamine secretion was determined as the percentage released into each supernatant based on the total histamine originally present in each aliquot of cells. Cell viability was determined as the percentage of peritoneal cells that excluded trypan blue. The percentage of mast cells was calculated by counting those stained metachromatically with toluidine blue. The average mast-cell size for each group was measured microscopically with an eyepiece micrometer grating. Since mast cells are the only peritoneal cells that contain histamine, a histamine standard curve was used to determine the histamine content per mast cell.

The 8 hr of food and water deprivation during exposure caused an average weight loss of 4.8 +/- 0.5% in the controls, 4.3 +/- 0.8% in those exposed at 2 mW/sq cm, and 4.3 +/- 0.3% in those exposed at 10 mW/sq cm. However, exposure to RFR at either level under these conditions had no apparent effects on the appearance or behavior of the rats. Blood

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smears taken immediately after sacrifice showed that the normally low basophil count (<1% of total leukocytes) was unaffected by the RFR. The results on several mast-cell parameters, presented in Table I of the paper, showed no significant differences among the groups exposed at 0, 2, and 10 mW/sq cm in percentage of cell viability, percentage of cells, amount of histamine per cell, and cell diameter (about 12.5 microns, with a range 18-10 microns). Notably, never found were giant mast cells (30-48 microns in diameter), an effect reported by Valtonen for RFR close to the LD-50 level (1966a, 1966b). The authors noted (without presenting data) that the intensity of toluidine blue metachromasia varied with each preparation, but that there was never a consistent RFR-related pattern.

Curves of histamine secretion vs 48/80 concentration for the sham and two RFR levels, displayed with SE bars in Fig. 2 of the paper, showed that mast cells from sham- and RFR-exposed rats responded to all concentrations of 48/80 in a similar manner. Curves of histamine secretion vs Con-A concentration, shown in Fig. 3, were similar, but with slightly larger (but nonsignificant) spreads in the range of low concentrations.

The other 2 rats of each group were anesthetized with pentobarbital immediately after RFR- or sham-exposure and their aortas were cannulated for blood-pressure measurements. Blood pressures and heart rates were recorded. After stabilization (1 hr), 48/80 was injected intravenously simultaneously into both rats and they were monitored for 2 hr. The results were exhibited in Table II.

The authors stated: "The initial blood pressures and heart rates (not shown) did not differ between the control and irradiated groups. The hypotensive response to 48/80 varied among the individuals; however, there were no significant differences due to irradiation of the animals."

In their discussion, the authors noted that the penetration depth at 2.45 GHz is about 2 cm (Johnson and Guy, 1972), so the blood basophils, cutaneous mast cells, and probably most of the peritoneal mast cells received direct RFR exposure. Nevertheless, the viability studies showed that the RFR did not greatly damage the cells of the peritoneal cavity or disturb the normal basophil count in the blood, findings in accord with previous in-vitro RFR data (Sawicki and Ostrowski, 1968; Ortner and Galvin, 1980). The authors also noted that the lack of effect on toluidine blue metachromasia and histamine content per cell indicated that normal uptake, metabolism, and storage of histamine and heparin were unimpaired, a finding contrary to that of Sawicki and Ostrowski (1968), who reported reduced metachromasia after 10 min of in-vitro exposure through air at 3 mW/sq cm. The absence of giant mast-cell formation was in agreement with the in-vitro findings of Sawicki and Ostrowski (1968) and Ortner and Galvin (1980), leading the authors to suggest that this effect may only occur in vivo under conditions approaching lethality (Valtonen, 1966a, 1966b).

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The authors also stated: "The present in vivo irradiation data now confirm our previous findings in vitro which showed that microwave radiation did not affect the complicated secretory pathways of these activators (Ortner and Galvin, 1980). Furthermore, we have shown that after intravenous injection of 48/80, the in vivo secretory response of the basophils and mast cells was unimpaired. This indicated that these cells are not adversely affected by any secondary factors potentially brought about by the radiation (e.g., release of hormones, neurotransmitters, etc.)."

CRITIQUE: Use of the Student t-test by the reviewer on the mast-cell data in Table I verified that the changes among the three groups were not significant, as the authors indicated. From Table II, however, the initial mean-blood-pressure values and SEs for the 0 (N=8), 2 (N=7), and 10 (N=7) mW/sq-cm groups were 110.6 +/- 2.6, 90.0 +/- 5.9, and 106.4 +/- 4.0, respectively. By the t-test, the difference between the 0- and 2-mW/sq-cm groups was significant at the 1% level and the difference between the 2- and 10-mW/sq-cm groups was significant at the 5% level, but the difference between the 0- and 10-mW/sq-cm groups was not significant (p>0.05). Thus, the changes were not monotonic with dose, and may have been due to uncontrolled non-RFR factors. The responses to 48/80 shown in Table II for the three groups were 28.5 +/- 4.5, 28.0 +/- 7.1, and 36.4 +/- 2.5, respectively; by t-test, the differences among the groups were not significant (p>0.05), as stated by the authors.

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Galvin, M.J., M.J. Ortner, and D.I. McRee
STUDIES ON ACUTE IN VIVO EXPOSURE OF RATS TO 2450-MHZ MICROWAVE
RADIATION--III. BIOCHEMICAL AND HEMATOLOGIC EFFECTS

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AUTHOR ABSTRACT: Male rats were exposed to 2450-MHz cw microwave
radiation for 8 hr at incident power densities of 0 (sham), 2, or 10
mW/sq cm. Following exposure, rats were killed by decapitation, and
blood samples were collected for determination of hematocrit,
hemoglobin, red and white cell count, and differential white cell
percentages. The total red and white cell counts were not affected by
either exposure level. The blood hemoglobin level was also unaffected
by the 8-hr exposure, having a value of approximately 15.5 g% for all
three groups. The percentages of lymphocytes and neutrophils for both
exposed groups was similar to those of the sham group. The other cell
types were also unchanged by the microwave exposure. None of the serum
biochemistries examined were affected by either microwave exposure
level. These data therefore demonstrate that acute (8 hr) exposure to
2450-MHz cw microwave radiation has no effect on the hematologic and
biochemical parameters examined.

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Study Type: Immunology and Hematology, Physiology and Biochemistry;
IN VIVO; RAT
Effect Type: Effects of acute in-vivo RFR exposure on blood parameters
Frequency: 2.45 GHz
Modulation: CW
Power Density: 2, 10 mW/sq cm
SAR: 0.44, 2.2 W/kg

EXPOSURE CONDITIONS: As detailed in Ortner et al. (1981), groups of 8
male CD rats (mean weight 300 +/- 35 g) were concurrently sham-exposed
or exposed for 8 hr at 2 or 10 mW/sq cm in individual Styrofoam cages
arranged in an oval pattern around the axis of, and 155 cm below (in the
far field of), a standard-gain horn. The horizontal dimensions of the
cages were 10x20 cm, with the latter oriented parallel to the E-vector.
The narrower dimension did not permit the rat to orient itself
comfortably perpendicular to the E-vector and the vertical dimension (13
cm) permitted the rat to rear but not stand upright. The top and bottom
of each cage were plastic gratings to allow for ventilation and removal
of urine and feces.

Exposures were done within an anechoic chamber maintained at 24 deg C
and 65% relative humidity, and lighted from 6 am to 6 pm. At the
nominal mean power density of 10 mW/sq cm, the values around the oval
ranged from 8.1 to 10.9 mW/sq cm. For exposures at this mean value,
additional fans at cage level were operated to prevent heating from the
RFR absorber under the cages. SARs were determined from Durney et al.

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(1978), based on a prolate-spheroidal model. For a 320-g rat parallel to the E-vector, the SARs corresponding to 2 and 10 mW/sq cm were 0.44 and 2.2 W/kg. Such calculations were subsequently corroborated by calorimetric measurements (Smialowicz et al., 1979).

The rats were weighed immediately before and after RFR- or sham-exposure. Prior to exposure, they were kept within the anechoic chamber for at least 12 hr in group cages with food and water available ad libitum. They were then transferred to individual cages and the 8-hr exposures were started at 12:30 am, with food and water withheld. Exposures at 0 (sham), 2, and 10 mW/sq cm were conducted on successive days, for a total of 12 experiments.

OTHER INFORMATION: This study was the third in a series involving exposure of rats to 2.45-GHz RFR for 8 hr under similar conditions, the first study being by Ortner et al. (1981) on the effects of exposure on basophils and peritoneal mast cells, and the second, by Abhold et al. (1981), on the effects on thyroid and adrenal hormones.

As in Ortner et al. (1981), the 8 hr of food and water deprivation during exposure had no apparent effects on the appearance or behavior of the rats. All three groups exhibited comparable losses of body weight (<4%) following exposure. Deep colonic temperatures, measured in some rats immediately after exposure, averaged 38 deg C, with no significant differences among the groups.

Within 5-15 min after exposure, the rats were decapitated and blood samples were collected for determining hematocrits (Hct), red blood cell counts (RBC), white blood cell counts (WBC), hemoglobin levels (Hb), and differential white cell percentages. The remaining blood from each rat was centrifuged, and the serum was assayed for beta-glucuronidase, alkaline phosphatase, total protein concentration, lactic dehydrogenase activity, cholinesterase, and concentrations of sodium and potassium. Statistical inferences were made with Duncan's range test for comparing several means, with p<0.05 deemed significant.

The serum-biochemistry results for the groups exposed at 0, 2, and 10 mW/sq cm were displayed in Table I of the paper in terms of means and SEs. The authors stated that there were no significant differences among the three groups for beta-glucuronidase, alkaline phosphatase, cholinesterase, lactic dehydrogenase, or total protein. They also stated that there were no significant RFR-induced differences in sodium or potassium concentration among the groups.

The results on the hematopoietic system, displayed in Table II of the paper, showed no significant differences among the three groups for any of the parameters measured, i.e., Hct, Hb, RBC, WBC, and percentages of lymphocytes, neutrophils, and monocytes.

In their discussion, the authors noted that Deichmann et al. (1964) had reported the occurrence of leukocytosis, lymphocytosis, and neutrophilia in rats following exposure to pulse-modulated 24-GHz RFR at 10 mW/sq cm

(average) for 3 hr. In addition, increases in circulating erythrocytes, Hb concentration, and Hct were observed in Osborne-Mendel and CFN rat strains but not in the Fischer strain, with no explanation given for the strain differences in response. By contrast, Kitsovskaya (1964) observed hematologic changes in rats exposed to 3-GHz CW RFR at 40 and 100 mW/sq cm but found no changes for exposures at 10 mW/sq cm for 216 days, 1 hr/day. The results of the present study support the latter finding.

On the other hand, the authors also noted that Wangemann and Cleary (1976) found statistically significant changes in serum glucose, uric acid, and urea nitrogen for rabbits exposed for 2 hr to 2.45-GHz CW and pulsed RFR at 5, 10, and 25 mW/sq cm, but no changes in LDH, GOT, Na, or K. Fulk and Finch (1972) assayed various blood-serum constituents in rats exposed to 2.86-GHz pulsed RFR for 15 min at average power densities of 5, 10, 20, 50, and 100 mW/sq cm, and found significant changes of albumin and phosphorus only at levels that caused significant increases in body temperature (>50 mW/sq cm). Blood glucose levels were not altered. Lastly, the authors mentioned that in their second study (Abhold et al., 1981), serum adrenal steroid levels were altered by 8 hr of exposure of rats to 2.45-GHz CW RFR at 10 mW/sq cm, and that none of the serum constituents examined in the present study were affected by RFR exposure.

CRITIQUE: Regarding the serum-biochemistry results, use of the Student t-test by the reviewer on the data in Table I supported all of the negative findings except possibly for those on sodium and potassium ion concentrations. The mean Na+ concentrations and SEs for the 0, 2, and 10-mW/sq-cm groups were respectively 123.6 +/- 3.93 mM/1 (N=18), 130.1 +/- 2.04 mM/1 (N=17), and 117.6 +/- 5.02 mM/1 (N=19). The t-test indicated that the difference between the 0- and 2-mW/sq-cm groups and between the 0- and 10 mW/sq-cm groups were not significant but that the difference between the 2- and 10-mW/sq-cm groups was significant. The corresponding mean K+ concentrations were 5.6 +/- 0.22 (N=18), 6.2 +/- 0.18 (N=18), and 5.4 +/- 0.33 (N=20). By the t-test, the difference between the 0- and 2-mW/sq-cm groups was significant, as was the difference between the 2- and 10-mW/sq-cm groups, but the difference between the 0- and 10-mW/sq-cm groups was not significant. However, for both sodium and potassium ions, the changes with power density were not monotonic, a strong indication that the changes were not RFR-related, in consonance with the authors' statement.

Use of the t-test on the hematopoietic data in Table II yielded no significant differences among the three groups, as indicated by the authors.

Explanations for the apparently contrary findings among the various investigators, discussed by the authors as noted above, are difficult to reconcile because of differences in species, frequencies, modulations, exposure conditions, and biological methodologies.

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AUTHOR ABSTRACT: A cohort study was made on 2,043 infants born to 2,018
females registered as physiotherapists at the time of pregnancy during
1973 to 1978. The incidence of perinatal death, serious malformation,
short gestational duration, and low birth weight was slightly below the
expected with consideration given to maternal age and parity
distribution. Information on occupational exposure (use of shortwave,
microwave, and ultrasonic equipment, X-ray exposure, use of
electrostimulator or hexachlorophene-containing soaps) was obtained in a
case-control study within the cohort from mail questionnaires with a 93%
response rate. The only positive finding was a higher incidence of
shortwave equipment use among the females with a dead or malformed
infant than among controls. Various explanations for this finding are
discussed.

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Study Type: Human Studies; IN VIVO; HUMAN
Effect Type: Effect on pregnancy outcome of occupational exposure to
various agents, including RFR, among registered physiotherapists in
Sweden
Frequency: Unspecified, other than shortwave diathermy and microwave
diathermy
Modulation: Unspecified, but assumed to be that of the above diathermy
equipment
Power Densities: Unknown
SAR: Unknown

EXPOSURE CONDITIONS: Physiotherapis   .   re presumed to have been more
likely to have been exposed   ip   ly to various agents, including
RFR, than the general p   l   .   ever, in the cohort study, it was
not known whether each   '   y worked during her pregnancy, nor
whether she had used the equi   der study.

OTHER INFORMATION: To obtain information for the cohort study, a case-
control study was performed within the cohort, comparing cases (infants
with perinatal mortality and major malformations) with controls (normal
infants). Exposure for 37 selected cases and 74 controls was estimated
from answers to a questionnaire asking (in part):

"Did you, during the pregnancy, work with or in close proximity to the
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INFLUENCE OF 2.45-GHZ CW MICROWAVE RADIATION ON SPONTANEOUSLY BEATING
RAT ATRIA
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electrode can produce a local field enhancement of the order of 10 million (Guy, 1975), and that at low power densities, the enhanced field may not cause observable heating or tissue damage at the electrode tip, but can modify electrophysiological activity of neurons or cells (through induced currents or local microthermal heating) and thereby yield confusing results (Chou and Guy, 1978a).

They then concluded that:

"1. The bradycardia effect of microwave radiation may have been due to an induced-current artifact of the high concentration of KCl or the metal wire electrodes.

2. The Ringer's solution electrode with a conductivity close to that of tissue is a minimum-interfering electrode which should be used in future electromagnetic field studies."

CRITIQUE: The results of this study clearly indicate the perturbations introduced by the various types of electrodes used, a most important consideration in endeavoring to interpret the findings of others who used electrodes that might have been affected by RFR or might have altered the local fields in their vicinity.

It is interesting that from the graphs presented, the curves for groups E and F, recorded with the tension transducer, appeared to overlap most closely, possibly indicating that this recording technique was the least perturbing. Next were those done ultrasonically (groups C, D, and J), but the differences between RFR and control groups were also not significant. (The absence of change in group D during the first 10 min of RFR, noted above as an apparently significant difference from the control group, was not discussed by the authors and may have been anomalous; the first sentence quoted was obscure.) By contrast, even the two-part Ringer's solution electrode introduced significant artifact, though less than the immersed wire or the KCl electrode, which were comparable in effect.

The finding of no RFR-induced beat-rate changes in isolated frog hearts exposed to 2.45-GHz CW RFR at SARs of 2 and 8.55 W/kg when nonperturbing recording electrodes were used are consistent with the negative results of Galvin et al. (1982a) for spontaneously beating rat atria exposed in-vitro to 2.45-GHz CW RFR at 2 or 10 W/kg, but are at variance with those of Tinney et al. (1976) with isolated turtle hearts and Reed et al. (1977) with isolated rat hearts, who reported the occurrence of bradycardia at comparable SARs. However, the relevance of such negative or positive findings to possible cardiovascular effects on intact animals is unclear because of the absence of the rest of the autonomic nervous system and its regulatory functions. More relevant are the negative results of Chou et al. (1980b) on heart-beat rate of intact rabbits exposed to 2.45-GHz CW RFR at SARs in the heart up to 5 W/kg, and of Galvin and McRee (1981a), who found that exposure of normal and ischemic cat hearts in-vivo to 2.45-GHz CW RFR at 30 W/kg.

RFR exposure, then dropped 5 min later (after 15 min of RFR) to the same value as for group C and continued to decrease at about the same rate as group C for the remainder of the recording period. Based on the SEMs shown for both groups, the differences were significant during the first 10 min of RFR exposure but not at the other times during the recording period.

The results for group J (9 hearts), exposed at 2 W/kg, were displayed in Fig. 6 together with those of sham group C. Group J exhibited a linear decrease in mean percentage heart rate similar to that of group C, with no significant differences between the two groups.

For groups E and F, a tension transducer was used to measure the isometric contractile tension of heart muscle; a 1.5-g force was attached to the suture, providing a constant load to the heart. The hearts of group E (8) were sham-exposed and those in group F (15) were exposed at 8.55 W/kg. The results, displayed in Fig. 4, showed no significant differences between these groups.

For group G, a Ringer's solution electrode (a glass cylinder tapered to a tip at one end and filled with Ringer's solution), with a metal wire immersed to the tip, was used. The electrode for groups H and I was in two parts: a short Ringer's solution electrode filled with solution and a short metal wire attached at the surface of the solution and connected to a longer electrode also filled with solution. Groups G (10 hearts) and H (9 hearts) were exposed at 8.55 W/kg and group I (10 hearts) was sham-exposed. The results were displayed in Fig. 5. Once again, the control group exhibited a linear decrease in mean percentage change of heart rate and there were no significant differences among the groups until the onset of RFR at min 10. The curve for group G (recorded with the wire immersed in the solution) showed that significantly larger percentage changes had occurred during and after RFR exposure, decreasing by 66% at min 40 and by 85.6% of initial value at the end of the recording period. By contrast, the curve for group H (recorded with the two-part electrode) was above the control curve (smaller percentage changes) during the RFR period and below the control curve post-exposure until min 60, where they intersected, but the authors indicated that the differences between these two curves were not significant.

In their discussion, the authors stated: "We observed bradycardia only when recording via high-concentration KCl electrodes or metal-wire electrodes. Using other recording techniques, we saw no effect of microwaves on heart rate for either high or low values of SAR. It should be pointed out that this study was not designed to replicate any previous experiment. We used exposure parameters and recording techniques that were available to us."

They also noted that many investigators used the EEG, evoked potentials, and EKG to study the effects of RFR on nervous system function (Baranski and Edelwejn, 1974; Goldstein and Sisko, 1974; Gavalas et al., 1970; Frey, 1967) and on the heart (Frey and Seifert, 1968), and that metal electrodes were usually used. They indicated that a thin metal

cross-sectional area of the waveguide. The result for input and reflected powers of 0.3 and 0.01 W was 8.55 W/kg, one of the two values used; the other value was 2 W/kg.

OTHER INFORMATION: The objectives of this study were to observe the effects of RFR·on the beating rate of the isolated frog heart and to determine the influence of various recording electrodes on the results. Ten groups (A through J) of frogs (102 total) were studied. The heart of each was excised, placed in Ringer's solution, and allowed to recover from shock. Silk sutures were fixed to the aorta and the apex of the heart. The heart was placed horizontally on a Plexiglas holder, which was then inserted in the waveguide. The interval between killing and exposure was about 50 min. The beat rates of RFR- and sham-exposed hearts were recorded by the methods described below for 60 min after preparation. RFR exposures were for the 30-min interval starting at min 10 and ending at min 40 of the recording period. The results for each group were displayed graphically vs time (at 10-min intervals), not as mean heart rates, but as mean percentage changes in heart rate (+/- SEMs). The Mann-Whitney U-test was used for all statistical analyses.

For heart groups A and B, a glass electrode filled with 3M KCl solution was placed in the heart; another electrode against the waveguide wall served as the reference. The hearts in group A (10) were sham-exposed during the 60-min recording period; those in group B (11) were exposed at 8.55 W/kg (for the 30-min interval). The results for these groups were displayed in Fig. 2 of the paper. For both groups, the mean heart rate dropped by about 10% during the first 10 min of the recording period. For group A, the rate continued to decrease essentially linearly, by about 37% of its initial value at min 40, and by an additional 33% (to 70% of the initial value) during the remaining 20 min. For group B, however, the decrease was steeper while the RFR was on, by 73.5% of its initial value at min 40 (cessation of exposure), after which the decrease was slower, by an additional 6.5% (to 80% of initial value). The differences between the groups were statistically significant (p<0.05).

For groups C, D, and J, an ultrasonic transducer placed at the surface of the Ringer's solution served to record heart rate. The hearts of group C (10) comprised the sham group, those in group D (10) were exposed at 8.55 W/kg, and those in group J (9) were exposed at only 2 W/kg. The results for groups C and D were shown in Fig. 3. Group C yielded a linear percentage decrease in heart rate with time similar to that of group A. The results for group D were characterized by the authors as follows: "During the first 15 min of the exposure period, a decrement in the heart rate was observed. In the following 15 min, the slope of the heart rate for the exposed organs was similar to that of control group C. At the end of 1 h, the mean decreases in heart rate of groups C and D were 55% and 50%, respectively. No significant difference was observed between the two groups." For group D, however, Fig. 3 showed that the approximately 10% decrement seen in both groups at min 10 of the recording period (the start of RFR exposure) remained unchanged (no further decrease in heart rate) for the first 10 min of

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Yee, K.C., C.K. Chou, and A.W. Guy
EFFECT OF MICROWAVE RADIATION ON THE BEATING RATE OF ISOLATED FROG
HEARTS

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AUTHOR ABSTRACT: One hundred and two isolated frog hearts were divided
into ten groups and placed individually in a waveguide filled with
Ringer's solution and exposed to 2,450-MHz CW radiation at 2 and 8.55
W/kg. Heart rate was recorded using one of the following methods: 3-M
KCl glass electrode, ultrasound probe, tension transducer, Ringer's
solution glass electrode, and a metal wire inserted in the Ringer's
solution electrode. An accelerated decrease of heart rate was observed
only in those groups recorded using the 3-M KCl electrode and the metal
wire Ringer's solution electrode. No effect was found in the other
groups. These results indicate that bradycardia in isolated hearts
could be caused by electrode artifacts resulting from the
intensification of electromagnetic fields.

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Study Type: Cardiovascular Effects; Biorhythms; Exposure Methods,
Dosimetry, and Modeling; IN VITRO; FROG
Effect Type: Influence of electrodes on bradycardia reported to be
induced in isolated hearts by RFR
Frequency: 2.45 GHz
Modulation: CW
Power Density: Not indicated
SAR: 2 or 8.55 W/kg

EXPOSURE CONDITIONS: Exposures were done from below in a vertical
section of WR-284 rectangular waveguide (inside dimensions 7.2 cm x 3.4
cm) filled with Ringer's solution to a height of 6 cm, as described in
Chou and Guy (1978b). The solution was maintained at constant
temperature by an external circulation system. A quarter-wavelength
dielectric slab at the lower end of the section was used to match the
impedance of the solution to that of air and to seal the bottom of the
section. From Chou and Guy (1975), the complex dielectric constant of
the solution at 2.45 GHz was 74.3-j20.5, which yielded a penetration
distance of 1.65 cm. Thus, the 6-cm fluid column was essentially
equivalent to one of infinite length. A 3-mm hole was drilled in each
of the four walls of the waveguide at 1 cm above the dielectric slab for
a heart holder, and a Plexiglas chamber was glued to the outside of each
wall to accommodate the transducer used for recording the motion of an
isolated heart stretched perpendicular to the electric field component
of the TE10 waveguide mode.

SARs of the Ringer's solution at the location of the isolated heart (1
cm) were calculated from values of net forward (input minus reflected)
power, the attenuation constant and density of the solution, and the

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MERRITT
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BIOCHEMISTRY
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PULSED
RAT
RFR
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WEIGHT

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It is interesting to note that all of the negative findings above were for rats. By contrast, RFR-induced teratogenesis in the mouse was reported, for example by Berman et al. (1982). They exposed mice to 2.45-GHz RFR at 28 mW/sq cm (16.5 W/kg) for 100 min daily during gestation days 6-17 and observed significant growth retardation (about 10%) in the fetuses, an effect that persisted for at least 7 days after birth. This effect appears to have been thermally induced, a conclusion supported by the results of Inouye et al. (1982) and Nawrot et al. (1981). These differences in response between rats and mice may be an indication that neither species is a satisfactory surrogate for humans with regard to possible RFR teratogenesis.

In the present study, the values of cell numbers and sizes in Table 3 cited above appear to be incorrect. The total brain DNA values for the sham and RFR groups given in Table 1 were 0.33 and 0.34, respectively. Substitution of these values into the cell-number equation yields 53.23 and 54.84 rather than 53.56 and 55.07. Similarly, the corresponding values of total brain weight given in Table 1 were 73.0 and 69.8. Substitution of these and the presumably correct values of cell numbers into the cell-size equation yields 1.372 and 1.273 rather than 1.445 and 1.364. However, these differences do not materially affect the findings of this study.

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No. of cells = total brain DNA (mg) x 1000/6.2,

and the cell size (in ng/nucleus) from:

Cell size = total brain wt (g) x 1000/No. of cells,

the factor 6.2 above being the DNA content of a diploid nucleus in picograms.

The mean numbers of cells for the sham (N=108) and RFR (N=108) groups, displayed in Table 3 of the paper (with SEMs) respectively were 53.56 +/- 3.82 and 55.07 +/- 5.13, a nonsignificant difference. The corresponding cell sizes were 1.445 +/- 0.086 and 1.364 +/- 0.124, also a nonsignificant difference.

To determine the effects of RFR exposure on brain development, a regression of mean litter brain weight on mean litter body weight was calculated for the sham group. The resulting equation was:

Brain weight (g) = 0.04524 + (0.029 x body weight), r = 0.859,

which was graphed in Fig. 3. Scattered about the line were the mean values for the RFR group. Based on Edwards (1969), the criterion used for microencephalous litters was a regression line, shown in Fig. 3, two SEMs below the regression line for the sham group. All of the RFR mean values were above the criterion line, i.e., no litter was encephalous. The regression equation for the RFR group was:

Brain weight (g) = 0.0453 + (0.027 x body weight), r = 0.903.

In their discussion, the authors noted that unlike in other teratologic studies (Chernovetz et al., 1977, 1979), in which decreases in brain weight, body weight, and altered brain chemistry were reported for exposures of rats at intensities sufficient to induce substantial increases in body temperature, the rats in this study were exposed continuously at a relatively low SAR (insufficient to increase body temperature). The authors also noted that Jensh et al. found no significant teratogenic effects in rats exposed to 915-MHz RFR at 10 mW/sq cm (1982a) or to 2450-MHz RFR at 20 mW/sq cm (1983a), but that Shore et al. (1977) reported smaller brain and body weights in neonatal rats from dams exposed at 10 mW/sq cm to 2450-MHz RFR with their long axes parallel to the E-vector only. No differences in pup mortality or litter size were observed.

CRITIQUE: As indicated by the authors, their negative findings with rats support those of the investigators noted above. In addition, Jensh (1984a) exposed rats to 6-GHz RFR at 35 mW/sq cm (7.28 W/kg) and reported that the only effects observed were a slight but statistically significant growth retardation at term and a depression of term maternal monocyte count relative to controls. However, it is not clear that these differences were RFR-induced because there were also significant differences among control groups.

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to 70-90%, depending on body weight and orientation in the cage. From differential power measurements on rat carcasses of different weights, the mean fractions of guide-input power in 14 different orientations of each rat were plotted vs rat weight (Fig. 1 of the paper), from which a regression line was calculated. The equation for this line was:

Input power fraction absorbed = 0.433 + (0.0267 x weight in kg).

From Durney et al. (1980), p. 60, the incident average power density of circularly polarized RFR corresponding to 0.4 W/kg in a prolate-spheroidal model of a medium rat exposed end-on was about 2 mW/sq cm. The regression line was used to adjust the input power to maintain the SAR constant at 0.4 W/kg for each dam as its weight increased during the exposure period.

OTHER INFORMATION: All 20 rats were pregnant when delivered on gestation day 2. They were weighed, immediately placed randomly in the 10 RFR- and 10 sham-exposure waveguides, and exposed. They were reweighed every fourth day. On gestation day 18, the dams were euthanized by cervical dislocation, the uteri were quickly excised, and the fetuses were removed. After each fetus was weighed, its brain was dissected out, weighed, homogenized in ice-cold 0.25-M sucrose, and assayed for brain RNA, DNA, and protein.

The results were examined statistically by a weighted means analysis for unequal cells (Statistical Analysis System Supplementary Program). The means and SEMs of fetus body weight (g), brain weight (mg), DNA, RNA, and protein were presented in Table 1 for the RFR and sham groups. Brain DNA, RNA, and protein were expressed in both microgram/mg of tissue and mg/brain, with the authors noting: "The relevant expression of brain is amount per brain since DNA concentration falls with growth owing to increasing cell size and increasing noncellular myelin. Maturational deficits that affect cell number would be better reflected in amount per brain." There were no significant differences between the two groups (p>0.05) for any of the eight measures above (with N either 109 for each group or 108 when one sample was lost during processing).

The authors also noted: "Since there may be correlation among the measurements of the individual fetuses within a given litter, variance should be calculated from the means of the litters rather than from individual measurements (Abbey and Howard, 1973)." The point was illustrated in Fig. 2, which showed (separately for the RFR and sham groups) the mean fetus weights of the litters in increasing order, with their respective SEMs (and weight ranges) to indicate the influence of clustering. Some statistically significant differences in mean body weight among the litters of each group were clearly evident. The results for the eight measures on a litter basis (with 18 degrees of freedom) were presented in Table 2. Again there were no significant differences between the two groups (p values ranging from 0.27 to 0.94).

Based on formulas from Enesco and Leblond (1962), the number of brain cells (in millions) was calculated from:

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Merritt, J.H., K.A. Hardy, and A.F. Chamness
IN UTERO EXPOSURE TO MICROWAVE RADIATION AND RAT BRAIN DEVELOPMENT

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AUTHOR ABSTRACT: Timed-pregnancy rats were exposed in a circular
waveguide system starting on day 2 of gestation. The system operated at
2,450 MHz (pulsed waves; 8 microsecond PW; 830 pps). Specific
absorption rate (SAR) was maintained at 0.4 W/kg by increasing the input
power as the animals grew in size. On day 18 of gestation the dams were
removed from the waveguide cages and euthanized; the fetuses were
removed and weighed. Fetal brains were excised and weighed, and brain
RNA, DNA and protein were determined. Values for measured parameters of
the radiated fetuses did not differ significantly from those of sham-
exposed fetuses. A regression of brain weight on body weight showed no
microencephalous fetuses in the radiation group when using as a
criterion a regression line based on two standard errors of the estimate
of the sham-exposed group. In addition, metrics derived from brain DNA
(ie, cell number and cell size) showed no significant differences when
radiation was compared to sham exposure. We conclude that 2,450-MHz
microwave radiation, at an SAR of 0.4 W/kg, did not produce significant
alterations in brain organogenesis.

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Study Type: Teratology and Developmental Abnormalities, Nervous System;
IN VIVO; RAT
Effect Type: RFR-induced effects on in-utero brain development
Frequency: 2.45 GHz
Modulation: circularly polarized, 8-microsecond pulses at 830 pps
(0.0066 duty cycle)
Power Density: 2 mW/sq cm Av (estimated)
SAR: 0.4 W/kg

EXPOSURE CONDITIONS: Ten pregnant Sprague-Dawley rats, each in an
individual cylindrical Plexiglas cage within a circular-waveguide system
(Guy et al., 1979) were exposed for 24 hr/day to the RFR and 10
similarly housed rats were concurrently sham-exposed, starting on
gestation day 2 and ending on gestation day 18. The cages were large
enough to permit free movement of the rats. All 20 waveguides were in a
room maintained at 24 +/- 2 deg C and 50-60% relative humidity. Water
and food were provided freely during exposure via a bottle and food-
pellet holder decoupled from each cage and waveguide by quarter-
wavelength chokes to minimize external power losses.

The power absorbed by each rat was determined from measurements of
forward, reflected, and transmitted powers without and with the rat
present. An empty waveguide absorbed about 20% of the input power;
addition of the cage, water bottle, and feeder increased the value to
about 30%. The presence of a rat or rat model increased the absorption

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Shortwave equipment: daily/often/seldom/never
           Microwave equipment: daily/often/seldom/never
           Ultrasonic equipment: daily/often/seldom/never
           X-Ray equipment: daily/often/seldom/never
           Electrostimulator: daily/often/seldom/never"

All certified physiotherapists in Sweden are registered in a computer
file at the National Board of Health and Welfare, and identified by a
unique identification number. There is likewise a computerized register
of all deliveries in Sweden since January 1973, containing information
on the newborn including survival and possible malformations, plus each
mother's identification number. Cross-linking files between these
registers made it possible to identify a number of deliveries where the
mother was a registered physiotherapist at the time of delivery. This
cohort was then analyzed by comparison with the total Medical Birth
Register with respect to perinatal mortality and the presence of
malformations. The authors were careful to correct for age of the
mother, parity (first, second, third, etc., pregnancy), and hospital of
delivery (which especially influences the reported diagnosis of
malformations, notably minor ones).

The outcome of this carefully conducted cohort study showed that, for
the offspring of the physiotherapists, perinatal death rate was
slightly below the expected, but not significantly. The number of
offspring with a birth weight less than 2500 g and a gestation period
less than 38 wk was markedly less than that expected. The total number
of offspring with a malformation diagnosis was very near the expected.
The number of major malformations was, if anything, lower than expected.

The authors suggested that the excellent outcome of this cohort study
could have been the result of a "healthy worker" effect. Also,
exposure of the mothers was essentially unknown. They therefore
conducted a case-control study aimed at finding out if those cases of
perinatal mortality and major malformations in the cohort were
associated with excess occupational exposure.

For the case-control study, all infants with a major malformation and
all infants who died perinatally without a malformation were selected.
There were 37 mothers with such infants. For each, two controls were
chosen (74 mothers), matched for maternal age (+/- 2 yr), parity (1, 2,
3+), and time of delivery during the year (to compensate for seasonality
in work resulting from holiday periods). Each of the total of 111
mothers was sent an explanatory letter describing the study, and a
simple questionnaire. The questions sought information about occupation
during pregnancy, the part of the pregnancy worked, use of shortwave,
diathermy, ultrasonic, X-Ray, or electrostimulator equipment, use of
hexachlorophene-containing soap (a purported teratogen in humans and
therefore a potential positive-control agent), and anything else in the
work situation that the mother could remember as being relevant. There
were 103 responses to the questionnaire, a response rate of 93%. Of
these 103, 33 cases and 63 controls actually worked as physiotherapists

during the relevant pregnancy. These 96 constituted the population for the case-control study.

Results of answers to the questionnaire were presented in Table 4 of the paper. The responses were divided into Cases versus Control for location worked (e.g., hospital wards, private practice, etc.), and for use of the various equipment and soap referred to above. The following sub-table described use of shortwaves:

	Cases	Controls
never	15	25
seldom	7	29
often	2	5
daily	9	4

The authors chose to combine the categories "never" and "seldom", and to combine "often" and "daily", to reduce the table from four-by-two to two-by-two. This they tested with Fisher's Exact Test (1-tail), and found a statistically significant difference (P=0.03). A detailed examination of the diagnoses for the 11 cases of malformation or perinatal death for infants whose mothers had worked "often" or "daily" with shortwave equipment was unable to show any obvious patterns of damage. Similar grouping and testing for the other usage responses, including hexachlorophene-containing soap, yielded differences between cases and controls that were not statistically significant.

In their discussion, the authors carefully reviewed and interpreted the results of their investigation. They concluded that, as a group, the physiotherapists had a slightly better-than-expected outcome with respect to perinatal deaths and major malformations than did the general Swedish population in the same period. Among those physiotherapists who did give birth to a malformed or perinatally dead infant, there were indications, however, of a higher use (statistically significant) of shortwave equipment. The authors indicated that the results could have arisen at random, since the level of significance was borderline, but they found it difficult to reject the finding as a random phenomenon.

CRITIQUE: This paper provides an excellent example of a well-conceived and well-conducted epidemiologic investigation into the potentially hazardous effects of occupational exposure to nonionizing radiation. The study was performed in Sweden, where comprehensive and complete data files on many aspects of the economy and population are maintained in computers. The study group chosen, pregnant physiotherapists, was known to work with equipment emitting various forms of nonionizing radiation. All relevant computerized data base information was readily accessible to the investigators and essentially complete. This is in direct contrast to the relative inaccessibility and/or lack of completeness of data that poses problems in many similar studies (e.g., Hamburger et al., 1983; Pazderova, 1971; Cohen et al., 1977). The authors carefully reported their methodology and intermediate results in sufficient detail to permit checking of their statistical calculations. (These were

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correct.) Their overall findings appear valid. As a group, there was no evidence of any detrimental effects on pregnancy outcome such as increased perinatal mortality or malformations. The results of the case-control study did indicate a possible relationship between higher use of shortwave equipment and increased perinatal mortality and malformations. Because of the significance of these findings and the relatively small numbers of subjects in the case-control study, it is worthwhile performing a sensitivity analysis on the reported data.

In forming a two-by-two table for shortwave use, the authors obtained the following:

	Cases	Control	Total
never/seldom	22	54	76
often/daily	11	9	20
		Total	96

This yields a z-statistic for the Fisher Exact Test (Meddis, 1975) of 1.91, P=0.028 (1-tail), in agreement with the findings of the authors. Now consider the situation in which one of the respondents in the Case category is moved from a response of "often" to "seldom". The table now becomes:

	Cases	Control	Total
never/seldom	23	54	77
often/daily	10	9	19
		Total	96

This new table yields a z-statistic of 1.59, P=0.056. That is, a shift of just one response from "often" to "seldom" results in the loss of statistical significance (at the 5% level). A similar exercise wherein the Case responses remain unchanged but one response is moved from "seldom" to "often" in the Control group results in a z-statistic of 1.70, P=0.045, which is almost exactly at the (arbitrarily defined) margin dividing significance from nonsignificance (P=0.05). A shift of two responses yields z=1.49, P=0.068, which is nonsignificant. It is thus seen that, while the results presented by the authors are technically correct and the study has been performed with great care, the findings are critically dependent upon the accuracy of recollection of the respondents with regard to the frequency of use of the shortwave equipment. A shift of only one or two answers from the somewhat arbitrary distinction of "seldom" to "often" (or vice-versa) results in loss of statistical significance of the findings. For this reason, the finding of an association between increased maternal exposure to shortwave radiation and increased infant perinatal mortality and malformation should be taken as requiring further study with larger populations to yield greater statistical robustness.

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CHRONIC
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Williams, W.M., W. Hoss, M. Formaniak, and S.M. Michaelson
EFFECT OF 2450 MHZ MICROWAVE ENERGY ON THE BLOOD-BRAIN BARRIER TO
HYDROPHILIC MOLECULES. A. EFFECT ON THE PERMEABILITY TO SODIUM
FLUORESCEIN
Brain Res. Rev., Vol. 7, pp. 165-170 (1984a)

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AUTHOR SUMMARY: Significantly elevated levels of sodium fluorescein (MW
376) were found only in the brains of conscious rats made considerably
hyperthermic (colonic temperatures > 41.0 deg C) by exposure to ambient
heat (42 +/- 2 deg C) for 90 min or 2450 MHz CW microwave energy at 65
mW/sq cm (SAR about 13.0 W/kg) for 30 or 90 min. For microwave-exposed
rats, fluorescein levels within the cortex and hypothalamus appeared to
increase with increasing duration of exposure. This trend was not
apparent in the cerebellum or medulla. Exposure to ambient heat
resulted in increased fluorescein with [sic, presumably "within"] the
cortex, hypothalamus and medulla, but not the cerebellum, and, in
general, ambient heat was not as effective as microwave energy in
raising tracer concentrations within the brain. By far the greatest
elevation of fluorescein dye in the brain occurred in those animals
whose blood-brain barrier had been opened osmotically by intracarotid
injection of 10 M urea. It is suggested that increased levels of sodium
fluorescein found in the brain tissue of ambient heat and microwave-
exposed rats most likely represent technically derived artifact and not
a breakdown of the blood-brain barrier.

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Study Type: Nervous System; IN VIVO; RAT
Effect Type: Comparison of effects of microwave exposure, ambient heat,
and intravenously injected hyperosmolar urea on cerebral
microvasculature permeability to systemically circulating sodium
fluorescein, and of the effect of hyperthermia on circulating plasma
levels of sodium fluorescein
Frequency: 2.45 GHz
Modulation: CW
Power Density: 20 or 65 mW/sq cm
SAR: 4 or 13.0 W/kg

EXPOSURE CONDITIONS: Fisher-344 male rats were housed in individual
wire-mesh cages in animal quarters maintained at 23 +/- 1 deg C and a
normal 0600-1800 light cycle. During each day from 0900 to 1200 for at
least 7 days prior to exposure, the rats were acclimated to simulated-
exposure conditions by placing them individually and unrestrained within
8x8-inch Styrofoam boxes like those used for exposure. This treatment
was continued until colonic temperature, taken at the end of each 3-hr
daily session, was within the normal range for the rat (37-38 deg C).

On the day of an experiment, rats were acclimated and then either sham-
exposed or exposed dorsally to 2.45-GHz CW RFR in the far field (169 cm

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from an S-band Narda 644 standard-gain horn) at 20 or 65 (+/- 6) mW/sq cm for 30, 90, or 180 min within an anechoic chamber maintained at 24 +/- 1 deg C ambient temperature and 55-68% relative humidity. Other rats were similarly acclimated but exposed to heat for 30 or 90 (+/- 10) min in the anechoic chamber by raising the ambient temperature to 42 +/- 2 deg C.

OTHER INFORMATION: This paper is the first of a series of four on possible alterations of the blood-brain barrier (BBB) by exposure to RFR or ambient heat, as determined by various detection techniques. The companion papers are: Williams et al. (1984b, c, d).

Sodium fluorescein (NaFl) was used as a tracer in previous studies on effects of RFR on the BBB by Frey et al. (1975), and by Merritt et al. (1978). Both of these groups used anesthetized animals. Frey et al. (1975) claimed to see alterations of BBB permeability to NaFl under certain RFR-exposure conditions, but their results could not be confirmed by Merritt et al. (1978).

In the present study, fluorescein was used as the tracer in 29 rats (weighing 250-300 g) sham-exposed or exposed to RFR or ambient heat. Studies with urea as a positive-control agent instead of RFR or heat were carried out on three additional rats. Four to five days prior to experiments, an indwelling catheter was placed in the right jugular vein and exteriorized between the scapulae. The tip of the catheter was positioned at the juncture between the superior and inferior venae cavae. With this preparation, solutions could be injected directly into the conscious animal.

Within 15-30 seconds after exposure (as described above) or following an iv injection of 10-M urea to open the BBB osmotically, colonic temperature was measured, and within 2 min, infusion of 200 microliters of 0.5% NaFl and 1 ml of saline wash was begun. The infusion took 1 min. The tracer was allowed to circulate for 5 min, then the animal was anesthetized with 50 mg/kg of sodium pentobarbital, iv. Within 1-2 min of anesthesia, intracardiac perfusion with 300 ml of cold heparinized saline was carried out; the brain was rapidly removed; and portions of the cerebral cortex, hypothalamus, cerebellum, and medulla were removed. The portions were weighed, placed in vials containing 200 microliters of butanol, homogenized, and centrifuged. A 100-microliter aliquot was removed, placed in a tube containing 500 microliters of borate buffer, vortexed, and centrifuged again for 20 min or until the buffer (lower) phase was clear. Samples of this phase were then read on a Perkin-Elmer fluorescence spectrophotometer. Relative fluorescence intensity was measured at an excitation wavelength of 482 nm and at an emission wavelength of 520 nm. Standard curves (fluorescence intensity vs concentration in ng/ml) allowed derivation of the concentration of NaFl in the brain samples.

To prepare the calibration standards, a 5-microliter quantity of 0.5% NaFl was diluted in 1 ml of butanol containing a small amount of homogenized brain tissue. The solution was vortexed, centrifuged, and a

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500-microliter aliquot of the butanol phase was extracted and diluted in 2.0 ml of borate buffer (pH 10). Final standard dilutions ranged above and below NaFl concentrations in brain samples. These standard concentrations were 0.25, 2.5, 25, and 50 ng NaFl/ml.

Results of these measurements of NaFl concentration in brain samples following perfusion with saline were given in Table I of the paper. Significantly elevated levels of fluorescein ($P<0.05$ when compared with brain samples from the same regions of sham-exposed animals) were found in the brains of rats exposed at 65 mW/sq cm for 30 or 90 min; for the urea (positive-control) animals; for the cortex, hypothalamus, and medulla, but not the cerebellum, of animals exposed to heat (42 +/-2 deg C); and for none of the brain samples of animals exposed to 20 mW/sq cm for 180 min. In general, ambient heat was not as effective as RFR energy in raising tracer concentration within the brain, and neither agent yielded elevations as great as the hyperosmolar solution of urea.

Studies were carried out on 3 additional rats to determine the effect of hyperthermia on circulating plasma levels of NaFl. Colonic temperatures were increased from normothermic levels (37-38 deg C) to 41.2-41.8 deg C in 30 min. Four other rats, treated identically but without exposure to hyperthermia, served as controls. Plasma concentrations (numbers not given in the text) were stated to be significantly higher ($P<0.05$) for the 3 rats exposed to ambient heat than for the controls. The mean plasma-concentration integral over the 5-min circulation period was 1020 g NaFl.s/ml for the hyperthermic rats and 838 g NaFl.s/ml for the controls. Using the argument that disruption of the BBB to NaFl would be expected to result in a disproportionate increase in the calculated ratio of measured brain tissue concentration of NaFl for the 5-min period:

$$(\text{brain-C,5})/(\text{integral of the plasma concentration}),$$

the authors calculated this ratio for cerebral cortex, hypothalamus, cerebellum, and medulla brain samples from each of the four sham- and three hyperthermic rats.

Differences between ratios were found not to be statistically significant when analyzed by the Mann-Whitney U-test. Because of this, the authors concluded that the increased levels of tracer found in the brains of rats made hyperthermic by ambient heat or by exposure to RFR were most likely the result of elevated circulating levels of NaFl due to reduced renal excretion. A second source of artifact might have been increased blood vascular space in the brain (BVS) resulting from moderate hyperthermia, but BVS was not determined in this experiment. Increases in circulating level of NaFl and BVS would both be expected to increase the residual amounts of tracer in the brain resulting from either pinocytotic uptake during the 5-min circulation period or from incomplete clearance of fluorescein from the lumen and luminal wall surface of cerebral vessels. Thus, they concluded that the increased levels of the tracer in the brain were not the result of alteration of the BBB permeability to NaFl.

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CRITIQUE: In general, use of conscious, unrestrained rats in this and the companion studies represents a significant advance over previous methods used to ascertain the effects of RFR on the blood-brain barrier. Effects of stress arising from handling, the exposure environment, and colonic-temperature measurement were minimized by acclimating the animals to all procedures, before the actual experiments, until colonic temperatures at the end of the conditioning period were in the normal range for the rat.

Regarding the dosimetry, the SARs were determined by colonic temperature rises in anesthetized rats as described in Lu et al. (1977), in which the rat orientation relative to the field vectors was not stated. Also, in the present and companion studies, each rat evidently was free to move about in its 8x8-inch box and probably varied its orientation randomly and considerably during exposure. However, based on prolate-spheroidal models of the rat (Durney et al., 1978, pp. 94-96), the difference in whole-body SARs for the long body axis of the rat parallel and perpendicular to the polarization plane (E and H polarizations) is small at 2.45 GHz. Thus, the time variations of SAR of the rats during exposure were probably minor.

The authors presented calculations of ratios of NaFl concentrations in brain tissue to integrals of NaFl concentration in plasma that indicated convincingly that BBB permeability to NaFl was not altered in hyperthermic rats. Therefore, it is somewhat surprising that they did not present similar results for the positive-control, hypertonic-urea rats. Demonstrating significant changes in this ratio for urea would have further strengthened their conclusions.

In general, their findings that levels of the tracer fluorescein are increased in the brains of rats made hyperthermic by exposure to RFR or ambient heat, and that these increases do not reflect a change in the BBB permeability but are rather an artifact of the technique, are likely to provide a means for explaining the apparently contradictory results of Frey et al. (1975) and Merritt et al. (1978).

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EFFECT OF 2450 MHZ MICROWAVE ENERGY ON THE BLOOD-BRAIN BARRIER TO
HYDROPHILIC MOLECULES. B. EFFECT ON THE PERMEABILITY TO HRP

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AUTHOR SUMMARY: Alteration of blood-brain barrier (BBB) permeability by
2450 MHz CW microwaves was assessed semi-quantitatively after
intravenous injection of horseradish peroxidase (HRP) and exposure of
conscious, unrestrained rats to incident power densities of 0, 20, or 65
mW/sq cm for 30, 90, or 180 min. Additional rats were exposed to
ambient heat (42 +/- 2 deg C) for 30 or 90 min. None of the brain
regions studied, with the exception of the normally leaky pineal gland,
showed extracellular HRP leakage attributable to microwave or thermally-
induced breakdown of the blood-brain barrier. The mean ratio of HRP-
labeled microvessel endothelium/total number of microvessels counted was
determined for each brain region. Mean values for the cortex,
hypothalamus, cerebellum and medulla of microwave-exposed and heated
rats were consistently below those of corresponding sham levels. This
decrease appeared to correlate inversely with power density and duration
of exposure. Statistically significant deviation (P<0.05) from sham
mean values occurred in the cortex, hypothalamus, cerebellum and medulla
of animals made hyperthermic with ambient heat or exposure to microwaves
at 65 mW/sq cm (specific absorption rate about 13.0 W/kg) for 30 or 90
min. Additionally, electron microscopic evaluation of ultrathin
sections taken from each of the 4 brain regions revealed no significant
extravasation of HRP indicative of microwave or ambient heat-induced
disruption of the blood-brain barrier.

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Study Type: Nervous System; IN VIVO; RAT
Effect Type: Comparison of the effects of microwave exposure and of
ambient heat on the permeability of the cerebral microvasculature to the
tracer horseradish peroxidase using light microscopy (including single-
blind analysis) and electron microscopy
Frequency: 2.45 GHz
Modulation: CW
Power Density: 20 or 65 mW/sq cm
SAR: 4 or 13.0 W/kg

EXPOSURE CONDITIONS: As described in Williams et al. (1984a), Fisher-
344 male rats were housed in individual wire-mesh cages in animal
quarters maintained at 23 +/- 1 deg C and a normal 0600-1800 light
cycle. During each day from 0900 to 1200 for at least 7 days prior to
exposure, the rats were acclimated to simulated-exposure conditions by
placing them individually and unrestrained within 8x8-inch Styrofoam
boxes like those used for exposure. This treatment was continued until
colonic temperature, taken at the end of each 3-hr daily session, was
within the normal range for the rat (37-38 deg C).

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On the day of an experiment, rats were acclimated and then either sham-exposed or exposed dorsally to 2.45-GHz CW RFR in the far field (169 cm from an S-band Narda 644 standard-gain horn) at 20 mW/sq cm for 180 min, or 65 (+/- 6) mW/sq cm for 30 or 90 min, within an anechoic chamber maintained at 24 +/- 1 deg C ambient temperature and 55-68% relative humidity. Other rats were similarly acclimated but exposed to heat for 30 or 90 (+/- 10) min in the anechoic chamber by raising the ambient temperature to 42 +/- 2 deg C.

OTHER INFORMATION: This paper is the second of a series of four on possible alterations of the blood-brain barrier (BBB) by exposure to RFR or ambient heat, as determined by various detection techniques. The companion papers are: Williams et al. (1984a, c, d).

Experiments with HRP were conducted on 20 conscious, unrestrained rats weighing between 250-300 g. (The numbers in the tables actually sum to 21 animals.) Three to five days prior to experiments, an indwelling catheter was implanted in the right jugular vein, enabling solutions to be injected directly into the conscious animal.

Marked hypotension had been reported in some strains of rats 2-3 min after iv injection of 5-10 mg HRP/100 g body weight (Deimann et al., 1976). Other toxic effects observed included signs of erythema and edema of paws, ears and snout; lethargy; and prostration. Occurrence of such effects in Fisher-344 rats would be a potential source of artifact. This possibility was investigated by the authors. They inserted indwelling catheters into the right jugular vein and femoral artery of six rats. After the rats recovered from anesthesia, four of them were exposed to RFR (65 mW/sq cm) for 30 or 90 min. The other two were sham-exposed. Following exposure, femoral blood pressure was monitored for 1 min prior to injecting a 0.5-ml solution of HRP at a concentration of 15 mg/100g body weight, and for up to 60 min following the injection.

Mean blood pressure remained virtually unchanged in all six animals. It was noted that the animal became noticeably less active on injection of the tracer, but did not display behavior indicative of illness, such as lowering of the head and sniffing. Toxicity was therefore not considered a problem at the levels of HRP used in the present study.

For the study on BBB effects proper, rats were exposed under one of the procedures described above under "Exposure Conditions". Within 15-30 seconds after terminating an exposure, colonic temperature was recorded. HRP, weighed and diluted in 0.5 ml of saline to give an injectable concentration of 15 mg/100 g body weight, was then injected iv at a constant rate of 0.6 ml/min and allowed to circulate for 60 min. The animal was then anesthetized with 50 mg/kg iv sodium pentobarbital, perfused intracardially with 50-75 ml of cold heparinized saline 1-2 min after anesthesia, and fixed by perfusion with 300 ml of cold 2% glutaraldehyde in 0.1 M cacodylate buffer and 5% dextrose. Brains were subsequently removed and 2-mm-thick sections of cerebral cortex, hypothalamus, cerebellum, and medulla were dissected and immersed in 2%

glutaraldehyde in 0.1 M cacodylate + 5% dextrose for 3 h at 4 deg C. The pineal gland was also removed and fixed.

Following rinsing with 5% dextrose in 0.1 M cacodylate buffer overnight, tissue sections were embedded, cut into 100-micron slices, and prepared for visualization of peroxidase reaction product by a modification of the technique of Reese and Karnovsky (1967). This procedure yielded four blocks of stained, re-embedded tissue for each brain region of each animal. Thick sections were cut from each block on an ultramicrotome and placed on glass slides. Each slide was given an identification number comprised of the rat number, the brain region, and the block number (1-4) for that region.

For light microscopy, approximately 450 slides were examined for signs of BBB breakdown. Each slide was renumbered with a code by an assistant beforehand to provide a single-blind format. To evaluate each slide, 50 microvessels less than 30 microns in diameter were randomly selected and counted. The whole tissue section was then scanned, and evidence of HRP extravasation was recorded. The microvessels were assessed as positive or negative with respect to the presence of HRP product in four categories: in microvessel- or surrounding perivascular structures; within microvessel endothelium (vesicles); within pericyte; around basement membrane or extravasation into surrounding neuropil. After all slides had been examined, code numbers were matched with slide numbers (revealing the identity of each slide) and a ratio was calculated for each category with respect to the total number of vessels counted per slide (usually 50). A mean ratio per category for each brain region was then calculated from the ratios for the four slides examined for each region. A mean of means (+/- SEM) for each category was calculated for each brain region by summing the means of all rats (n=4 or 5) in each respective exposure group.

Representative blocks for each brain region were selected from control, RFR-exposed, and ambient-heat-exposed groups and ultrathin sections of each block were cut and examined with an electron microscope.

Under light microscopy, the normally leaky pineal gland showed reaction product in both RFR- and sham-exposed rats. Of the other brain regions studied, none showed extracellular leakage of HRP that could be attributed to RFR- or thermally-induced breakdown of the BBB. A few microvessel endothelial cells with HRP-flooded cytoplasm were observed infrequently in 1-micron sections of brain from both RFR- and sham-exposed rats. HRP reaction product was seen more frequently within pericytes or immediately surrounding these cells at the bifurcation of small arterioles or precapillaries. Reaction product was sometimes present between the apposing folia of the cerebellum, and immediately below the pial membrane in cerebral cortex. Brown reaction product was also apparent around a few small vessels in the arcuate nucleus, and especially around vessels of the median eminence in both RFR- and sham-exposed rats. (Examples of such observations were presented in Figs. 1-3 of the paper.) These observations were confirmed by electron microscopy (exemplified in Figs. 5-7).

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The results of the single-blind analysis were given in Tables I, II, and III for the five groups (sham, RFR at 20 mW/sq cm for 180 min, RFR at 65 mW/sq cm for 30 min, RFR at 65 mW/sq cm for 90 min, and ambient heat for 90 min). Mean ratios representing extravascular leakage of HRP into the surrounding neuropil were zero for the cortex, cerebellum, and medulla of all five groups and for the hypothalamus of the two 65-mw/sq-cm groups and the heat group. The hypothalamic ratios for the sham and 20 mW/sq-cm groups were small, comparable, and derived from a single rat in each group. By contrast, the pineal ratios $+/-$ SEMs for the five groups were 0.325 $+/-$ 0.132 (4 rats), 0.280 $+/-$ 0.082 (4), 0.318 $+/-$ 0.107 (4), 0.570 $+/-$ 0.013 (3), and 0.320 $+/-$ 0.122 (3), respectively. The mean ratios for HRP-labeled pericytes obtained from cerebral cortex, hypothalamus, cerebellum, and medulla of the three RFR groups and the heat group were consistently lower than the corresponding values for the sham group. This was also true for the mean ratios of HRP-labeled endothelium.

In their discussion, the authors stated: "This study not only failed to show an increase in BBB permeability to HRP following exposure to ambient heat or microwaves, but actually showed a reduced uptake of the tracer by the brain, i.e., cerebral microvessels...This reduced uptake appears to be a direct result of decreased formation of pinocytotic vesicles. Lipid insoluble molecules, including sucrose, cross the microvessel endothelium by vesicular transport (appropriate references cited). The observed reduction in vesicular transport of HRP would, therefore, explain the reduced permeability-surface area product (PA) for C-14 sucrose noted in those rats exposed to microwaves at 65 mW/sq cm for 30 min (Williams et al., 1984c)." The authors also noted that significantly depressed ($P<0.05$) pinocytotic activity was only evident in rats exposed to RFR at 65 mW/sq cm for 30 or 90 min or to ambient heat (42 $+/-$ 2 deg C) for 90 min, but that suppression may begin when brain temperatures exceed normothermic levels by as little as 1 deg C or less.

CRITIQUE: In general, the use of conscious, unrestrained rats in this and the companion studies represents a significant advance over previous methods used to ascertain the effects of RFR on the blood-brain barrier. Effects of stress arising from handling, the exposure environment, and colonic-temperature measurement were minimized by acclimating the animals to all procedures, before the actual experiments, until colonic temperatures at the end of the conditioning period were in the normal range for the rat.

Regarding the dosimetry, the SARs were determined by colonic temperature rises in anesthetized rats as described in Lu et al. (1977), in which the rat orientation relative to the field vectors was not stated. Also, in the present and companion studies, each rat evidently was free to move about in its 8x8-inch box and probably varied its orientation randomly and considerably during exposure. However, based on prolate-spheroidal models of the rat (Durney et al., 1978, pp. 94-96), the difference in whole-body SARs for the long body axis of the rat parallel and perpendicular to the polarization plane (E and H polarizations) is

small at 2.45 GHz. Thus, the time variations of SAR of the rats during exposure were probably minor.

Effects on the BBB (with HRP as the tracer) were previously reported for rats and Chinese hamsters exposed to 2.8-GHz RFR at 10 mW/sq cm for 2 hr (SAR about 2.5 W/kg for the rat). Albert (1979) and Albert and Kerns (1981) had found an increase in pinocytotic vesicles with HRP, which they interpreted as an increase in BBB permeability. By contrast, the present authors reported a significant decrease at an SAR of 13 W/kg, and a non-significant reduction of uptake by endothelial pinocytotic vesicles at 4 W/kg. However, in both of the earlier studies, the reported effects were also seen in some of the sham-exposed animals. Differences in the pre-exposure treatment of the animals and in the preparation of the brain samples by the two laboratories may be significant factors that contributed to the disparity in findings.

The present study was meticulous in reducing potential artifact, by experimentally ensuring that the HRP concentration used was not toxic (for Fisher-344 rats) and by using blind analysis to avoid potential bias on the part of the observer recording leakage of HRP from the vascular space. The authors were also careful to distinguish between exogenous peroxidase (from HRP) and the possible presence of endogenous peroxidase, which might have confounded the results obtained by Albert and Kerns (1981). The findings of the present study are therefore all the more credible.

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Radio Sci., Vol. 12, No. 6S, pp. 147-156 (1977)

the paper (with SEMs), were negative for the cortex and cerebellum, and positive for the hypothalamus and medulla. The delta-t values for the RFR- and heat-exposed groups did not differ significantly from those for the sham-exposed groups except for: the cortical value of the 65-mW/sq-cm, 30-min group; the hypothalamic value of the 20-mW/sq-cm, 180-min group; the cerebellar value of the 65-mW/sq-cm, 90-min group; and the cerebellar and medullar values of the high ambient-temperature group.

For individual rats exposed to RFR at 20 or 65 mW/sq cm or to ambient temperature of 33 or 43 deg C, each of its regional brain temperatures was plotted against its colonic temperature. The data for the four regions were shown separately in Figs. 6-9. Collectively, the points for each region clearly showed that brain and colonic temperature were linearly related. Regression lines were calculated and used to estimate mean regional brain temperatures for rats involved in the sodium-fluorescein (NaFl), horseradish-peroxidase (HRP), and C-14-sucrose tracer studies (described in the companion papers Williams et al., 1984a, b, c). These estimated regional brain temperatures (+/- SEMs) were exhibited in Table III.

The Spearman rank correlation coefficient, rs, was then calculated and used to assess ´between-group´ correlations of tracer levels within cerebral cortex, hypothalamus, cerebellum, and medulla with regional brain temperature from groups sham-exposed or exposed to RFR at 20 or 65 mW/sq cm for 30, 90, or 180 min. The resulting rs values were presented in Table IV. For the three groups assayed for NaFl concentrations after exposure at 20 mW/sq cm for 180 min or at 65 mW/sq cm for 30 or 90 min, the values of rs for the cortex, hypothalamus, cerebellum, and medulla were 0.800 (p<0.01), 0.720 (p<0.01), 0.623 (p<0.05), and 0.653 (p<0.01), respectively. (The critical values of rs at p=0.05 and p=0.01 were 0.456 and 0.645, respectively.) For the four groups assayed for HRP uptake after sham-exposure or exposure at 20 mW/sq cm for 180 min or exposure at 65 mW/sq cm for 30 or 90 min, the rs values for the cortex, cerebellum, and medulla were each 1.00 (p<0.05); the value for the hypothalamus, 0.800,was not significant (p>0.05). (The critical rs value at p=0.05 was 1.00.) For the two groups assayed for the sucrose permeability surface-area product (PA) after sham-exposure or exposure at 65 mW/sq cm for 30 min, the respective rs values were 0.399 (ns), 0.708 (p<0.05), 0.732 (p<0.05), and 0.851 (p<0.01). (The critical values of rs at p=0.05 and 0.01 were 0.643 and 0.833.) For the same groups assayed for C-14 uptake ratio, the corresponding rs values were 0.631 (ns), 0.708, 0.827, and 0.827, the latter three significant at the 5% level.

In discussing their results, the authors summarized the results of the companion papers (Williams et al., 1984a, b, c) involving the use of the tracers NaFl, HRP, and C-14 sucrose to study the effects of RFR and ambient heating of rats on their BBBs. They noted the apparent correlation between altered levels of tracer within the brain and elevation of brain temperature, and that the principal determinants of brain temperature include metabolic rate of brain tissue, rate of cerebral blood flow, and temperature of arterial blood, the last being

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The results (Table I of the paper) revealed the presence of a thermal gradient within the rat brain. In all groups, superficial regions of cerebral cortex and cerebellum were cooler than the deeper hypothalamus and medulla. The mean values and SEMs in deg C (and number of rats) for the cortex, hypothalamus, cerebellum, and medulla of the rats sham-exposed for 30 min were 36.5 +/- 0.11 (11), 37.3 +/- 0.02 (11), 36.6 +/- 0.10 (9), and 37.3 +/- 0.09 (9), respectively. The mean colonic temperature for this group was 37.0 +/- 0.09 (11). The corresponding results for the group sham-exposed for 90 min were 36.7 +/- 0.08 (10), 37.5 +/- 0.11 (10), 36.9 +/- 0.10 (10), and 37.6 +/- 0.10 (10), with a colonic temperature of 37.1 +/- 0.10 (11); the values for the group (5 rats) sham-exposed for 180 min were 36.5 +/- 0.16, 37.5 +/- 0.10, 36.8 +/- 0.09, and 37.6 +/- 0.11, with a colonic temperature of 37.3 +/- 0.11. Exposures to RFR and high ambient temperature yielded similar differences in regional brain temperature superposed on higher base levels, as discussed below.

For the 5-rat group exposed to RFR at 20 mW/sq cm for 30 min, the respective brain-region values were 37.2 +/- 0.08, 38.0 +/-0.08, 37.4 +/- 0.08, and 38.2 +/- 0.09, with a colonic temperature of 37.8 +/- 0.08. For the 5-rat group exposed at 20 mW/sq cm for 90 min, the results were 37.5 +/- 0.10, 38.2 +/- 0.11, 37.6 +/- 0.18, and 38.2 +/- 0.09; those for the 5-rat group exposed at 20 mW/sq cm for 180 min were 37.2 +/- 0.13, 37.9 +/- 0.09, 37.6 +/- 0.17, and 38.0 +/- 0.10. The mean colonic temperatures for these groups were 37.9 +/- 0.11 and 37.8 +/- 0.05, respectively.

The patterns were qualitatively similar for the groups exposed at 65 mW/sq cm but at higher base temperature. The group exposed at this level for 30 min yielded values of 39.9 +/- 0.19 (7), 41.2 +/- 0.18 (7), 40.5 +/- 0.16 (6), and 41.4 +/- 0.19 (6), with a colonic temperature of 40.9 +/- 0.13 (7); the values for the group exposed at this level for 90 min were 42.4 +/- 0.39 (8), 43.4 +/- 0.40 (8), 42.8 +/- 0.47 (6), and 43.7 +/- 0.49 (6), with a colonic temperature of 43.3 +/- 0.39 (8).

The mean temperatures in the cortex, hypothalamus, cerebellum, medulla, and colon for the group (8 rats) exposed to ambient temperature of 42 +/- 2 deg C were, respectively, 42.6 +/- 0.35, 43.1 +/- 0.39, 42.8 +/- 0.32, 43.3 +/- 0.35 and 43.2 +/- 0.36, again a similar pattern.

Statistical analysis of the results above indicated that the mean regional brain temperatures for all five RFR groups were significantly higher (U=0, p<0.05) than the corresponding values for the sham-exposed groups, as were the colonic temperatures. To quantify the relationship of regional brain temperatures with colonic temperature, the differences:

$$(delta-t) = (brain-t) - (colon-t)$$

were calculated for each region, with a negative value indicating that the mean colonic temperature was higher than that mean regional brain temperature. The results for all nine groups, presented in Table II of

EXPOSURE CONDITIONS: As described in Williams et al. (1984a), Fisher-
344 male rats were housed in individual wire-mesh cages in animal
quarters maintained at 23 +/- 1 deg C and a normal 0600-1800 light
cycle. During each day from 0900 to 1200 for at least 7 days prior to
exposure, the rats were acclimated to simulated-exposure conditions by
placing them individually and unrestrained within 8x8-inch Styrofoam
boxes like those used for exposure. This treatment was continued until
colonic temperature, taken at the end of each 3-hr daily session, was
within the normal range for the rat (37-38 deg C).

On the day of an experiment, rats were acclimated and then either sham-
exposed or exposed dorsally to 2.45-GHz CW RFR in the far field (169 cm
from an S-band Narda 644 standard-gain horn) at 20 or 65 (+/- 6) mW/sq
cm for 30, 90, or 180 min within an anechoic chamber maintained at 24
+/- 1 deg C ambient temperature and 55-68% relative humidity. Other
rats were similarly acclimated but exposed to heat for 30 or 90 (+/- 10)
min in the anechoic chamber by raising the ambient temperature to 42 +/-
2 deg C.

OTHER INFORMATION: This paper is the fourth of a series of four on
possible alterations of the blood-brain barrier (BBB) by exposure to RFR
or ambient heat, as determined by various detection techniques. The
companion papers are: Williams et al. (1984a, b, c).

The present study was devoted to measurements of local temperatures in
the cortex, hypothalamus, cerebellum, and medulla, and of colonic
temperature of conscious rats within 30-90 seconds after completion of
exposure to: RFR (2.45 GHz) at 0 (sham) or 20 mW/sq cm (SAR about 4
W/kg) for 30, 90, or 180 min; RFR at 65 mW/sq cm (SAR about 13 W/kg) for
30 or 90 min; or ambient heat at 42 +/- 2 deg C for 90 min. For this
purpose, two nylon screws, each having a hole through its center, were
surgically implanted and anchored under anesthesia in the head of each
rat, one screw (5.0 mm long) 4.0 mm anterior to the lambdoid suture and
1.5 mm left of the midline, and the other (5.5 mm long) 3.0 mm posterior
to the suture and 3.0 mm left of the midline. Recovery from the surgery
usually occurred within two weeks. Rats that exhibited altered
behavior, high temperature, or continued weight loss by the end of this
period were excluded from the study. Equilibration and handling were
done daily. Sixty-six rats (age 3-6 months) were studied.

Right after exposure, cortex temperature was recorded by rapidly
inserting a modified YSI hypodermic thermistor (which has a time
constant of 0.1 second and achieves 99% of its final value within 0.5
seconds) through one of the screws to a depth of 2 mm. Hypothalamic
temperature was then recorded by lowering the probe to a depth of 9 mm.
The temperatures of the cerebellum and medulla were recorded by using
the same procedure with the other screw. Colonic temperature was taken
immediately after completing the brain-temperature measurements. In
most cases, the last measurement was completed within 55-65 seconds.
Presumably, the data were analyzed with the non-parametric Mann-Whitney
U-test used in the companion studies.

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Williams, W.M., S.-T. Lu, M. del Cerro, and S.M. Michaelson
EFFECT OF 2450 MHZ MICROWAVE ENERGY ON THE BLOOD-BRAIN BARRIER TO
HYDROPHILIC MOLECULES. D. BRAIN TEMPERATURE AND BLOOD-BRAIN BARRIER
PERMEABILITY TO HYDROPHILIC TRACERS
Brain Res. Rev., Vol. 7, pp. 191-212 (1984d)

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AUTHOR SUMMARY: Measurement of temperature within the cerebral cortex,
hypothalamus, cerebellum and medulla of rats sham-, heat- or microwave-
exposed revealed the presence of a thermal gradient within the brain.
In all groups, cerebral cortex and the cerebellum were cooler than the
deeper hypothalamus and medulla. Exposure to 2450 MHz CW microwaves or
ambient heat (42 +/- 2 deg C) resulted in measurable elevation of
regional brain temperature, but without alteration of temperature
gradients normally observed within the brain. Exposure to 20 mW/sq cm
(SAR about 4 W/kg) for 30, 90 or 180 min induced a small, but
significantly (U=0, P<0.05) increased temperature of the colon, and in
each region of the brain studied. Exposure to an incident power density
of 65 mW/sq cm (SAR about 13.0 W/kg) for 30 or 90 min or to ambient heat
(42 +/- 2 deg C) for 90 min resulted in a substantially greater thermal
response as indicated by higher colonic and brain temperatures.

Comparison of regional brain temperature with individual colonic
temperatures is expressed as (delta-t) = (brain-t) - (colon-t). In
general delta-t values for ambient heat or microwave-exposed rats did
not differ significantly from those of sham-exposed animals. Exposure
to microwaves or ambient heat did not alter the general relationships
between regional brain and colonic temperatures, i.e., cortical and
cerebellar temperatures were always below and hypothalamic and medullary
temperatures always above corresponding colonic temperatures.

The plotted temperature data (brain vs colonic temperature) indicate a
linear relationship between brain and colonic temperatures. Levels of
sodium fluorescein (NaFl), horseradish peroxidase (HRP) and C-14 sucrose
(described in preceding papers) within the brain show a high correlation
(P<0.05) with brain temperature. Suppression [sic; presumably should
read "alteration"] of blood-brain barrier permeability to hydrophilic
tracers was most pronounced at brain temperatures exceeding about 40 deg
C and is demonstrated to be temperature dependent.

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Study Type: Nervous System; IN VIVO; RAT
Effect Type: Regional brain temperatures, colonic temperature, and RFR-
induced changes thereof, and relationship to alterations of the blood-
brain barrier
Frequency: 2.45 GHz
Modulation: CW
Power Density: 20 and 65 mW/sq cm
SAR: 4 and 13 W/kg

WILLIAMS
PLATNER
MICHAELSON

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BIOCHEMISTRY
BBB
BRAIN-UPTAKE-INDEX
CARDIOVASCULAR
CW
HEMATOLOGY
HYPERTHERMIA
IN-VIVO
NERVOUS-SYSTEM
RAT
RECTAL
TRACER

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Preston, E. and G. Prefontaine
CEREBROVASCULAR PERMEABILITY TO SUCROSE IN THE RAT EXPOSED TO 2,450-MHZ
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In the present study, injection of the tracer as a bolus into the jugular vein also avoided the sudden, large increase of blood pressure in the brain produced by arterial injection in the Oldendorf et al. (1970) technique. Thus, much credence can be given to the authors' conclusion quoted just above, except for qualifying the last statement therein by including exposure duration, at least for 65 mW/sq cm (30 min), since 90-min exposures at this power density rendered the rats severely hyperthermic. With regard to hyperthermia, it is noteworthy that the results of the fourth study (Williams et al., 1984d) demonstrated high correlations between tracer uptake and regional brain temperature.

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Acta Neuropathol. (Berl.), Vol. 57, pp. 255-262 (1982)

rats, the concentration of which is the denominator of the initial BVS estimate.

They indicated that elevated plasma integrals and tracer concentrations in whole blood were consistently found in the rats exposed to RFR or heat for 90 min, with colonic temperatures of all exceeding 41.5 and usually above 42 deg C, and that definite changes in renal function could occur at such temperatures. Thus, without discounting possible changes in sucrose distribution among the kidneys, liver, and muscle tissue, they ascribed the increased circulatory levels of sucrose primarily to reduction of renal clearance. In support of this hypothesis, they determined endogenous creatinine levels as an index of renal function from plasma samples collected from several sham-exposed and 90-min-hyperthermic (exceeding 42 deg C) rats. The mean creatinine concentrations (mg/ml serum) for 3 samples from each group were 0.3 +/- 0.17 and 1.2 +/- 0.12 mg%, respectively, suggesting significantly reduced glomerular filtration rates in these hyperthermic rats.

Because of the occurrence of impaired renal function in the severely hyperthermic rats, the authors regarded the BBB findings for these rats as unreliable, but indicated that this situation was avoided for the group rendered moderately hyperthermic. They therefore concluded that the arterial-integral method is a valid approach to calculating PAs in unrestrained conscious animals subjected to hyperthermic levels (by either heat or RFR) that do not impair renal function or alter tracer levels in plasma. They also stated:

"Our results, which confirm those previously reported by Gruenau et al. (1982) and Preston (1982), clearly demonstrate that exposure of conscious rats to 2450 MHz microwave energy at 20 or 65 mW/sq cm does not increase the permeability of the blood-brain barrier to sucrose."

CRITIQUE: Regarding the dosimetry, the SARs were determined by colonic temperature rises in anesthetized rats as described in Lu et al. (1977), in which the rat orientation relative to the field vectors was not stated. Also, in the present and companion studies, each rat evidently was free to move about in its 8x8-inch box and probably varied its orientation randomly and considerably during exposure. However, based on prolate-spheroidal models of the rat (Durney et al., 1978, pp. 94-96), the difference in whole-body SARs for the long body axis of the rat parallel and perpendicular to the polarization plane (E and H polarizations) is small at 2.45 GHz. Thus, the time variations of SAR of the rats during exposure were probably minor.

In general, use of conscious, unrestrained rats in this and the companion studies represents a significant advance over previous methods used to ascertain the effects of RFR on the blood-brain barrier. Effects of stress arising from handling, the exposure environment, and colonic-temperature measurement were minimized by acclimating the animals to all procedures, before the actual experiments, until colonic temperatures at the end of the conditioning period were in the normal range for the rat.

The authors indicated that evidently as colonic temperature neared or exceeded about 41.5 deg C, plasma-sucrose levels increased significantly above those for the sham group. This point was illustrated in Fig. 1 with representative plots of plasma-sucrose concentration (from samples taken periodically for 20 min) vs time after injection for a rat exposed at 65 mW/sq cm for 90 min and a sham-exposed rat. The two curves were similar (both exponentially decreasing), with the one for the RFR rat above that for the sham rat. (The integrals of plasma concentration were respectively 1.2 and 0.73 giga-dpm.s/ml.) The authors noted that these increased levels of circulating (C-14) sucrose constituted a potentially biasing artifact in calculations of PA and uptake ratio, and therefore they limited the 30-min-RFR group to those rats whose colonic temperatures remained below 41.3 deg C and whose concentration-vs-time profiles were within the range for sham-exposed rats. On this basis, the mean (+/- SEM) plasma integrals for the sham, 30-min-RFR, and 90-min-RFR groups were respectively 0.738 (+/- 0.099), 0.76 (+/- 0.054), and 1.231 (+/- 0.256) giga-dpm.s/ml. The difference between the 30-min-RFR and sham groups was not significant (U=10, P>0.557), whereas the plasma integrals for the rats in the 90-min-RFR group were significantly elevated above sham levels (U=0, P=0.014).

The mean values (+/- SEMs) of arterial blood pressure, pulse rate, and hematocrit (HCT) for the sham group, the groups exposed at 65 mW/sq cm for 30 and 90 min, and the groups subjected to 42 deg C ambient temperature for 30 and 90 min were presented in Table III. The mean HCTs for the five groups were 40 +/- 0.40 (6 rats), 41 +/- 0.86 (4 rats), 43 +/- 0.71 (4 rats), 43 +/- 0.88 (3 rats), and 43 +/- 1.53 (3 rats), respectively. In their discussion, the authors stated that "mean hematocrit levels for 90 min hyperthermic rats are slightly elevated above those of sham-exposed animals (see Table III), but differences are not significant enough to account for the large increase in circulating tracer seen in these animals." (By Student t-test, the last three values were significantly higher than the value for the sham group, i.e., the HCT level of the 30-min-heat group was also significantly elevated.)

The authors did not discuss the blood-pressure or pulse results. The mean blood pressures (mm Hg) for the respective groups were 128 +/- 1.98 (7 rats), 131 +/- 3.75 (4 rats), 163 +/- 12.65 (4 rats), 131 +/- 3.72 (5 rats), and 161 +/- 6.6 (4 rats). By t-test, the values for both 90-min groups were significantly higher than for the sham group. Corresponding mean pulse rates (beats/min) were 446 +/- 17.2, 386 +/- 12.8, 491 +/- 61.1, 401 +/- 17.1, and 486 +/- 47.5. The only significant difference from the sham group was the lower mean rate for the 30-min-RFR group.

In discussing their findings, the authors noted that as expected, BVS estimates for the rats subjected to moderate hyperthermia (about 41 deg C) were slightly elevated above normothermic levels, indicating increased vascular volume, but that mean BVS levels for severely hyperthermic rats (exceeding about 42 deg C) were unexpectedly less than or equal to estimates for sham-exposed rats. They ascribed the latter finding to significant elevations of sucrose in the whole blood of these

in which values of brain-C,20; blood-C,20; and the integral were mean data derived from the 20-min control group, and the BVS,init values were for each brain region of the control and heated groups. The values of parenchyma concentration at the end of the 5-min interval (paren-C,5) were then calculated by inserting the resulting PA values for each brain region into:

(paren-C,5) = PA x (integral of plasma-C over the 5-min period).

A more accurate value of BVS than BVS,init was then calculated from:

BVS = [(brain-C,5) - (paren-C,5)]/(blood-C,5),

and a process involving "reiterative nonlinear least squares fits to triple exponential curves, such that subsequent values deviated from the preceding value by 1% or less" was used to obtain final BVS values. Lastly, mean BVS values obtained from averaged final values were used with data from RFR- and sham-exposed groups to calculate regional PA values for each group. The data from all studies were analyzed with the non-parametric Mann-Whitney U-test for differences in distribution. Tables used were exact probabilities calculated for groups not exceeding 8 and 20 subjects (Siegel, 1956).

The mean values (+/- SEMs) of BVS for cortex, hypothalamus, cerebellum, and medulla were presented in Table I for the sham group and the groups exposed to heat for 30 and 90 min (4 rats per group). The mean regional BVS values for the 30-min-heat group were slightly but consistently higher than the corresponding values for the sham and 90-min-heat groups; the mean values for the 90-min-heat group except for the cortex were lower than those for the sham group; the differences were not statistically significant. (Presumably, because the changes were nonmonotonic with increasing heat, they were not heat-induced.)

The mean values (+/- SEMs) of PA for each region were presented in Table II for the sham group and the groups exposed to RFR at 65 mW/sq cm for 30 and 90 min (4 rats per group). The regional PA values for the 30-min-RFR group were consistently lower than the corresponding values for the sham and 90-min-RFR groups. Statistical treatment of the data showed that the decreases for the 30-min-RFR group were significant for the hypothalamus, cerebellum, and medulla (all at U=0, P=0.014) but that the decreases for the cerebral cortex were not significant (U=6, P=0.343).

The differences between corresponding values for the 90-min-RFR and sham groups were not significant. However, the authors noted (without presenting data) that two of the rats of this RFR group attained colonic temperatures below 42.5 deg C and yielded lower PA values than the other two rats in the group, whose colonic temperatures reached 43.0 and 43.4 deg C. Also, the lower PA values were within the range obtained for the 30-min-RFR group.

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Within 5-10 seconds after injection, the femoral catheter was disconnected from the transducer and 0.1-ml samples of whole blood were bled periodically into microcentrifuge tubes for 20 min (totaling less than 2 ml). At this time, the rat was decapitated, its brain was removed, and the arachnoid-pial membrane was peeled off. Rectangular 3x6-mm strips of left and right cerebral cortex, the whole hypothalamus, half the cerebellum, and a 4x4-mm strip of the medulla were removed, weighed, and placed in tared scintillation vials and reweighed. Each sample was incubated overnight at 55 deg C with Fisher Scintigest Tissue Solubilizer, held overnight in the dark with Packard Dimilume 30 added, and assayed for radioactivity in counts per min (cpm) with a Beckman LS 250 Liquid Scintillation Counter with automatic quench compensation.

For each rat, all the blood samples except the last were centrifuged, and 0.05-ml aliquots of plasma were withdrawn and placed in separate scintillation vials. A 0.01-ml aliquot of whole blood from the last sample was placed in a separate vial. To each vial, 0.6 ml of Scintigest tissue solubilizer and 0.3 ml of isopropyl alcohol were added, and the vials were incubated overnight at 55 deg C. Hydrogen peroxide (0.1 ml of a 30% solution) was added to the whole-blood vial and allowed to react for 2 hr at 55 deg C. The vials were then held overnight in the dark with Dimilume 30 added and assayed for radioactivity.

Cpm values for brain, plasma, and whole blood were converted to disintegrations per min (dpm) by the use of a separate quench curve for each region, and the following concentrations (C) of C-14 sucrose were determined for each rat: (1) brain-C,20 in dpm/g (at 20 min, the time at which the last blood sample was drawn and the rat decapitated) for cortex, hypothalamus, cerebellum, and medulla; (2) the integral of plasma-C over the 20-min period (dpm.s/ml), using the data from the periodically drawn samples; and (3) blood-C,20 (dpm/ml).

The blood vascular space (BVS) in ml of blood per gram of brain was calculated from rats in separate experiments to correct for non-parenchymal (intravascular) sucrose. In these experiments, rats were sham-exposed or subjected to ambient heating to attain colonic temperatures approximating those obtained by exposure at 65 mW/sq cm for 30 or 90 min. However, blood samples were collected for only 5 min before decapitation. For each control and heated rat, the ratio of brain-C,5 to blood-C,5 for each brain region was taken as an initial estimate of BVS (BVS,init) for that region:

$$BVS,init = (brain-C,5)/(blood-C,5).$$

To correct for sucrose loss from the intravascular compartment during the 5-min sampling period, an initial permeability-surface area (PA) product was calculated from (Preston and Prefontaine, 1980):

$$PA = [(brain-C,20) - (blood-C,20 \times BVS,init)]/(integral of plasma-C),$$

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similarly acclimated but exposed to heat for 30 or 90 (+/- 10) min in the anechoic chamber by raising the ambient temperature to 42 +/- 2 deg C.

OTHER INFORMATION: This paper is the third of a series of four on possible alterations of the blood-brain barrier (BBB) by exposure to RFR or ambient heat, as determined by various detection techniques. The companion papers are: Williams et al. (1984a, b, d).

The authors noted that Oscar and Hawkins (1977), who used the brain-uptake-index (BUI) technique of Oldendorf (1970), had reported that BBB permeability to mannitol and inulin in the rat could be increased by exposure to 1.3-GHz CW or pulsed RFR at an average power density of 3 mW/sq cm, that attempts by Merritt et al. (1978) to replicate these results using identical exposure parameters and conditions were unsuccessful, and that in another attempt with 2.45-GHz RFR, Preston et al. (1979) were unable to obtain significant changes in cerebral permeability to mannitol. They also noted that Oscar et al. (1981), using the in-vivo C-14-iodoantipyrine technique, had obtained increased cerebral blood flow from RFR exposure, which could affect BUI estimates of BBB permeability.

In the present paper, the results obtained with the arterial-integral method of Rapoport et al. (1979) were described. In this method, the single radiotracer C-14 sucrose (which normally crosses the intact BBB in negligible amounts) is injected intravenously as a bolus in treated and sham-treated animals; serial blood samples are taken; the brain is removed; the C-14 activity of samples of blood plasma, whole blood, and regional brain tissues are determined by liquid scintillation counting; and the data are used to quantitate the effect of treatment on the integrity of the BBB as described below. The three advantages cited by the authors for this method were: elimination of the biasing effect of transient changes in blood flow by the use of a plasma-time integral, accuracy equal to or exceeding the BUI technique, and adaptability for use with unanesthetized, unrestrained animals.

Twenty-four rats (280-340 g) were studied. Indwelling catheters were implanted into the right jugular vein and femoral artery 2-4 days before experiments. The proximal tip of the femoral catheter was advanced to within 1-2 mm of the juncture of the internal iliacs. Within 15-30 seconds after RFR-, sham, or heat exposure, colonic temperature was recorded and the conscious rat was rapidly transferred to an open Styrofoam box, where the jugular catheter was attached to an injection syringe via a polyethylene extension tube containing 10 microcuries of C-14 sucrose in 0.2 ml of sterile 0.9% NaCl (prepared 15 min before the end of exposure) and 0.2 ml of saline wash separated from the tracer bolus by a small air bubble. Injections were performed 4-6 min after the end of exposure. In addition, after exte rizing the distal 18 cm of the femoral catheter and flushing with 0.2 ml heparinized saline, the catheter was attached to a transducer for recording the blood pressure before, during, and after bolus injection.

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AUTHOR SUMMARY: Intravenously injected C-14 sucrose was used as a small
molecular weight (342 daltons), hydrophilic tracer for determination of
2450 MHz CW microwave and ambient heat effects on rat blood-brain
barrier permeability in the cerebral cortex, hypothalamus, cerebellum
and medulla. The tracer was injected 4 min following exposure of
conscious, unrestrained rats to microwaves at 0 or 65 mW/sq cm for 30 or
90 min (SAR about 13.0 W/kg) or to ambient heat (42 +/- 2 deg C) for 90
min.

Comparison of mean permeability-surface area products (PA) and uptake
ratios between sham and microwave-exposed animals revealed a
statistically significant (P<0.05) decrease of both PA and uptake ratios
for the hypothalamus, cerebellum and medulla of rats exposed to
microwaves for 30 min. This decrease was not apparent for rats exposed
to microwaves for 90 min. A pertinent observation, with regard to the
latter group of animals, was the increased circulation level of the
tracer when colonic temperature was raised to approximately 41.4 deg C
or higher.

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Study Type: Nervous System; IN VIVO; RAT
Effect Type: Alterations of the blood-brain barrier by RFR or heat, as
determined by changes in permeability to C-14 sucrose
Frequency: 2.45 GHz
Modulation: CW
Power Density: 65 mW/sq cm
SAR: 13.0 W/kg

EXPOSURE CONDITIONS: As described in Williams et al. (1984a), Fisher-
344 male rats were housed in individual wire-mesh cages in animal
quarters maintained at 23 +/- 1 deg C and a normal 0600-1800 light
cycle. During each day from 0900 to 1200 for at least 7 days prior to
exposure, the rats were acclimated to simulated-exposure conditions by
placing them individually and unrestrained within 8x8-inch Styrofoam
boxes like those used for exposure. This treatment was continued until
colonic temperature, taken at the end of each 3-hr daily session, was
within the normal range for the rat (37-38 deg C).

On the day of an experiment, rats were acclimated and then either sham-
exposed or exposed dorsally to 2.45-GHz CW RFR in the far field (169 cm
from an S-band Narda 644 standard-gain horn) at 65 (+/- 6) mW/sq cm for
30, 90, or 180 min within an anechoic chamber maintained at 24 +/- 1 deg
C ambient temperature and 55-68% relative humidity. Other rats were

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the most significant parameter that determines heat dissipation in the rat brain. They also stated the following:

"An early consideration in this study, with regard to possible causes of increased BBB permeability reported in the literature, was that regional or whole brain loss of thermoregulatory ability might precede or accompany breakdown of the barrier. Conceivably, apparent changes in permeability to a substance may be concomitant with a measurable degree of tissue heating. Those regions of the brain presenting greatest change in BBB permeability might therefore exhibit a somewhat greater heat load following exposure to microwaves...Animals exposed to a relatively low power density (20 mW/sq cm) reflected a small, but significant increment in temperature of the colon and of each region of the brain studied. At this incident power level, tissue heating is effectively minimized by the animal's thermoregulatory capacity, even after an exposure lasting 180 min...With exposure of sufficient duration, the thermoregulatory response to a high intensity microwave field, such as 65 mW/sq cm is not adequate to maintain brain or colonic temperatures within the normal range."

They concluded that at 20 mW/sq cm, physiological response mechanisms are more than adequate for maintaining body temperatures in the rat, including those of the brain, well within tolerable limits, but that exposure to intense fields (e.g., 65 mW/sq cm) for long durations (90 min) could approach or exceed such limits.

CRITIQUE: Regarding the dosimetry, the SARs were determined by colonic temperature rises in anesthetized rats as described in Lu et al. (1977), in which the rat orientation relative to the field vectors was not stated. Also, in the present and companion studies, each rat evidently was free to move about in its 8x8-inch box and probably varied its orientation randomly and considerably during exposure. However, based on prolate-spheroidal models of the rat (Durney et al., 1978, pp. 94-96), the difference in whole-body SARs for the long body axis of the rat parallel and perpendicular to the polarization plane (E and H polarizations) is small at 2.45 GHz. Thus, the time variations of SAR of the rats during exposure were probably minor.

In general, use of conscious, unrestrained rats in this and the companion studies represents a significant advance over previous methods used to ascertain the effects of RFR on the blood-brain barrier. Effects of stress arising from handling, the exposure environment, and colonic-temperature measurement were minimized by acclimating the animals to all procedures, before the actual experiments, until colonic temperatures at the end of the conditioning period were in the normal range for the rat.

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APPENDIX B

CUMULATIVE LIST OF ANALYSES BY TOPIC

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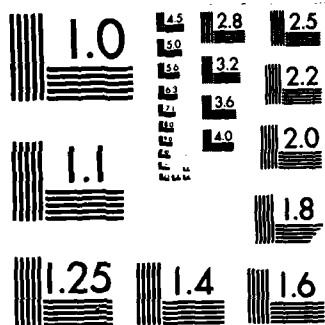ELDS (Correspondence)
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